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(54) **PREVENTIVES/REMEDIES FOR GLAUCOMA**

(57) An agent for the prophylaxis and treatment of glaucoma, which contains a compound having a Rho kinase inhibitory activity, particularly an agent for the prophylaxis and treatment of glaucoma, which contains a compound of the formula (I)



wherein each symbol is as defined in the specification, as the compound having a Rho kinase inhibitory activity, is provided. The agent for the prophylaxis and treatment of glaucoma of the present invention is a novel agent for the prophylaxis and treatment of glaucoma and has intraocular pressure lowering action, optic disc blood flow improving action and aqueous humor outflow promoting action.

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Description**Technical Field**

5 [0001] The present invention relates to an agent for the prophylaxis and treatment of glaucoma. More specifically, the present invention relates to an agent for the prophylaxis and treatment of glaucoma, which comprises a compound having a Rho kinase inhibitory activity as an active ingredient.

Background Art

10 [0002] Glaucoma is caused by an abnormally high internal pressure of the eyeball, wherein the abnormally high pressure makes the eye grow dim or hurts the eye, which in turn fails the eyesight little by little possibly into blindness. Normally, an aqueous humor continuously circulates in the eyeball and maintains a constant intraocular pressure (10 - 20 mmHg). The pressure is maintained by the circulation of the blood and lymphocytes, elasticity of the eyeball wall, the 15 performance of the control nerves and the like. An abnormality in any of them results in a rise of the intraocular pressure, which may develop glaucoma.

20 [0003] With the aim of preventing the intraocular pressure from rising or lowering an intraocular pressure that went up, for the prophylaxis and treatment of glaucoma, various drugs have been used. Known eye drops for the therapy of glaucoma include sympathetic agonists such as epinephrine, dipivefrine and the like. Due to mydriatic action, however, these eye drops enhance angle closure when administered to treat narrow angle glaucoma, and may cause not only an acute rise of the intraocular pressure, but also hypertension and pigmentation deposit. In addition, the parasympathetic 25 agonists such as pilocarpine and the like cause side effects such as dark visual field due to miosis and congested eye, iris cyst, posterior synechia, cataract, retinal detachment and the like after a long-term use. Moreover, β -adrenalin blockers such as timolol, pindolol and the like have been widely used, because they lower intraocular pressure by inhibiting the production of aqueous humor without acting on pupils. However, their use is limited, because β -adrenalin blockers have been reported to cause side effects such as local dry feeling of the eye, allergic blepharitis, superficial keratitis and the like, as well as systemic side effects such as bradycardia, heart failure, asthmatic fit and the like. These side 30 effects prevent application of the blockers to patients suffering from such symptoms. A recent suggestion of an aqueous humor outflow promoting effect of α 1-adrenalin blockers also suggests potential use of bunazosin hydrochloride and the like as a new therapeutic agent of glaucoma (Ikuo Azuma, Folia Ophthalmol. Jpn., 42, 710-714, 1991). However, the α 1-adrenalin blockers are inevitably associated with conjunctival injection and miosis due to their vasodilating action.

35 [0004] In the meantime, a compound having a Rho kinase inhibitory activity has been reported to show a hypotensive effect on various hypertension model animals (Masayoshi Uehata, et al., Nature 389, 990-994, 1997). The Rho kinase has been confirmed to be present in corneal epithelial cells (Nirmala SundarRaj, et al., IOVS, 39(7) 1266-1272, 1998). However, it is unknown if Rho kinase is present in other ophthalmic tissues.

40 [0005] The pharmaceutical use of the compound having a Rho kinase inhibitory activity is disclosed in WO98/06433, and, as a use in the ophthalmic area, is taught to be useful for retinopathy. However, WO98/06433 does not disclose its usefulness against glaucoma or description suggestive of the effect.

45 [0006] As a compound having a Rho kinase inhibitory activity, a compound of formula (I) to be mentioned later has been reported (WO98/06433). The compound of formula (I) has been already known to be useful as an agent for the prophylaxis and treatment of disorders of circulatory organs such as coronary, cerebral, renal, peripheral artery and the like (e.g., a therapeutic agent of hypertension, a therapeutic agent of angina pectoris, a therapeutic agent of renal and peripheral circulation disorder, a suppressive agent of cerebrovascular contraction and the like), which is potent and long lasting, and also as a therapeutic agent of asthma (JP-A-62-89679, JP-A-3-218356, JP-A-4-273821, JP-A-5-194401, JP-A-6-41080 and WO95/28387).

50 [0007] However, these compounds of the formula (I) are not disclosed to be useful for glaucoma, and there is no description suggestive of such usefulness.

Disclosure of the Invention

55 [0008] The present invention aims at solving the above-mentioned problems and provides a novel agent for the prophylaxis and treatment of glaucoma, which is superior in a prophylactic and therapeutic effect on glaucoma.

[0009] The present inventors have conducted intensive studies and found that a compound having a Rho kinase inhibitory activity also has an intraocular pressure lowering action, an optic disc blood flow improving action and an aqueous outflow promoting action, and that it is useful for the prophylaxis and treatment of various types of glaucoma, which resulted in the completion of the present invention.

[0010] Accordingly, the present invention provides the following.

(1) An agent for the prophylaxis and treatment of glaucoma, which comprises a compound having a Rho kinase inhibitory activity.

(2) The agent for the prophylaxis and treatment of glaucoma of (1) above, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I) wherein

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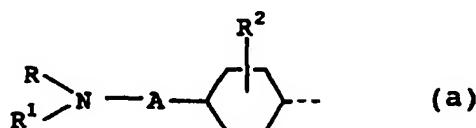
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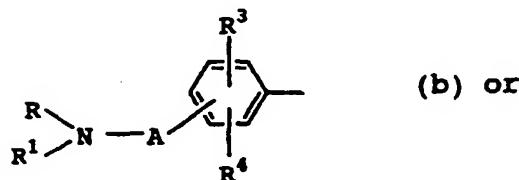
Ra is a group of the formula

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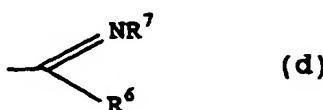
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R

in the formulas (a) and (b),
is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula

45

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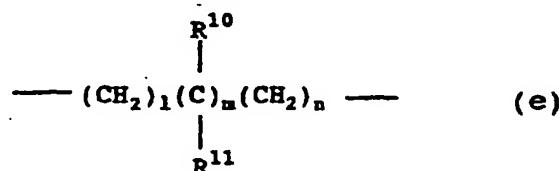
R¹

wherein R⁶ is hydrogen, alkyl or formula : -NR⁸NR⁹ wherein R⁸ and R⁹ are the same or different and each is hydrogen, alkyl, aralkyl or phenyl, R⁷ is hydrogen, alkyl, aralkyl, phenyl, nitro or cyano, or R⁶ and R⁷ in combination show a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R and R¹ in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted

nitrogen atom.

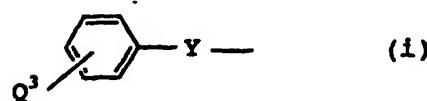
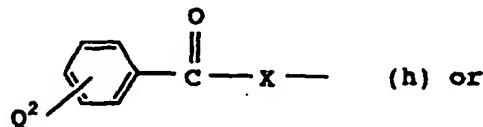
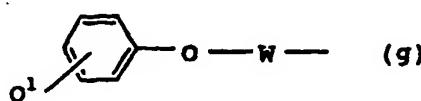
R² is hydrogen or alkyl,
R³ and R⁴ are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkythio, aralkylthio, carboxy, alkoxy-carbonyl, carbamoyl, alkylcarbamoyl or azide, and
A is a group of the formula



wherein R¹⁰ and R¹¹ are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-alkyl, carboxy or alkoxy carbonyl, or R¹⁰ and R¹¹ show a group which forms cycloalkyl in combination and I, m and n are each 0 or an integer of 1-3,

in the formula (c),
is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl,

phthalimidoalkyl, amidino or a group of the formula



wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxy carbonyl alkyl, α -aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl, Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thienvinylmethyl.

Q is hydrogen, halogen, hydroxy, aralkyloxy or trienylmethyl,
W is alkylene.

W is alkylene,
 $\text{O}^2 = \text{A} = \text{A}$

Q² is hydrogen, halogen, hydroxy or aralkyloxy.

X is alkylene.

Q³ is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tet-

rahydropyridazin-6-yl;
and Y is a single bond, alkylene or alkenylene, and in the formula (C),
a broken line is a single bond or a double bond, and

5 R⁵ is hydrogen, hydroxy, alkoxy, alkoxy carbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;
Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc is an optionally substituted heterocycle containing nitrogen,

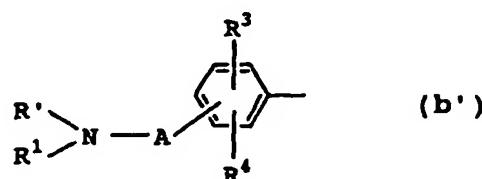
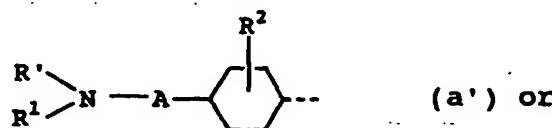
an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

10 (3) The agent for the prophylaxis and treatment of glaucoma of (1) or (2) above, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



20 wherein

Ra' is a group of the formula



40 wherein

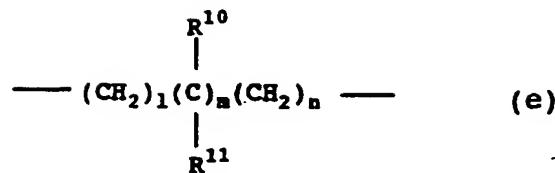
R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

45 R¹ is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R' and R¹ in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R² is hydrogen or alkyl,

50 R³ and R⁴ are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxy-

A is a group of the formula



10 wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-alkyl, carboxy or alkoxy carbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and I , m and n are each 0 or an integer of 1-3.

15 Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
 Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

(4) The agent for the prophylaxis and treatment of glaucoma of (1) above, wherein the compound having a Rho kinase inhibitory activity is (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid addition salt thereof.

(5) The agent for the prophylaxis and treatment of glaucoma of (1) above, which is administered to a local site in the eye.

(6) The agent for the prophylaxis and treatment of glaucoma of (5) above, which is in the form of an eye drop.

(7) A pharmaceutical composition for the prophylaxis and treatment of glaucoma, which comprises a compound having a Rho kinase inhibitory activity and a pharmaceutically acceptable carrier.

(8) The pharmaceutical composition for the prophylaxis and treatment of glaucoma of (7) above, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)



35 wherein each symbol is as defined above, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

40 (9) The pharmaceutical composition for the prophylaxis and treatment of glaucoma of (7) or (8) above, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



50 wherein each symbol is as defined above, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

(10) The pharmaceutical composition for the prophylaxis and treatment of glaucoma of (7) above, wherein the compound having a Rho kinase inhibitory activity is (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid addition salt thereof.

(11) The pharmaceutical composition for the prophylaxis and treatment of glaucoma of (7) above, which is for administration to local site in the eye.

(12) The pharmaceutical composition for the prophylaxis and treatment of glaucoma of (11) above, which is in the form of an eye drop.

(13) A method of the prophylaxis and treatment of glaucoma, which comprises administering an effective amount of a compound having a Rho kinase inhibitory activity to a patient.

5 (14) The method of the prophylaxis and treatment of glaucoma of (13) above, wherein the compound having a Rho kinase inhibitory activity is an aide compound of the following formula (I)



15 wherein each symbol is as defined above, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

(15) The method of the prophylaxis and treatment of glaucoma of (13) or (14) above, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



25 wherein each symbol is as defined above, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

30 (16) The method of the prophylaxis and treatment of glaucoma of (13) above, wherein the compound having a Rho kinase inhibitory activity is (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoy)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid addition salt thereof.

35 (17) The method of the prophylaxis and treatment of glaucoma of (13) above, wherein the administration to a patient is that to a local site in the eye.

(18) The method of the prophylaxis and treatment of glaucoma of (17) above, wherein the administration to a patient is by instillation.

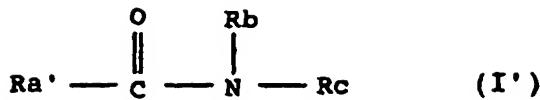
40 (19) Use of a compound having a Rho kinase inhibitory activity for the production of an agent for the prophylaxis and treatment of glaucoma.

(20) The use of (19) above, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)



50 wherein each symbol is as defined above, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

(21) The use of (19) or (20) above, wherein the compound having a Rho kinase is an aide compound of the following formula (I')



10 wherein each symbol is as defined above, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

(22) The use of (19) above, wherein the compound having a Rho kinase inhibitory activity is (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexane-carboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid addition salt thereof.

15 (23) The use of (19) above, wherein the agent for the prophylaxis and treatment of glaucoma is for administration to a local site in the eye.

(24) The use of (23) above, wherein the agent for the prophylaxis and treatment of glaucoma is in the form of an eye drop.

20 (25) A commercial package comprising a pharmaceutical composition for the prophylaxis and treatment of glaucoma of any of (7) to (12) above, and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for the prophylaxis and treatment of glaucoma.

Brief Description of the Drawings

25 [0011]

Fig. 1 is a graph showing the effect of the eye drop of Example 1 on the normal intraocular pressure, wherein the ordinate shows intraocular pressure, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop of Example 1 and ○ shows control eye (n=6, * p<0.05, ** p<0.01, *** p<0.001).

30 Fig. 2 is a graph showing the effect of the eye drop of Example 1 on the optic disc blood flow kinetic, wherein the ordinate shows relative optic disc blood flow, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop of Example 1 and ○ shows control eye (n=6, * p<0.05, ** p<0.01, *** p<0.001).

35 Fig. 3 is a graph showing the effect of Compound A on ciliary muscle contraction by carbachol, wherein the ordinate shows contraction rate of ciliary muscle, the abscissa shows concentration of carbachol, ○ shows control, ● shows addition of 1×10^{-5} M Compound A, ■ shows addition of 3×10^{-6} M Compound A and ▲ shows addition of 1×10^{-6} M Compound A.

40 Fig. 4 is a graph showing the effect of the eye drops of Example 2 [0.1% compound A] (a) and Example 5 [0.1% compound C] (b) on the normal intraocular pressure, wherein the ordinate shows intraocular pressure, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop and ○ shows control eye (n=6, * p<0.05, ** p<0.01 Student's t-test).

45 Fig. 5 is a graph showing the effect of the eye drops of Example 3 [0.03% compound A] (a) and Example 4 [0.03% compound B] (b) on the normal intraocular pressure, wherein the ordinate shows intraocular pressure, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop and ○ shows control eye (n=6, * p<0.05 Student's t-test).

50 Fig. 6 is a graph showing the effect of the eye drops of Example 6 [0.03% compound C] (c) and Example 7 [0.03% compound D] (d) on the normal intraocular pressure, wherein the ordinate shows intraocular pressure, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop and ○ shows control eye (n=6, * p<0.05, ** p<0.01, *** p<0.001 Student's t-test).

55 Fig. 7 is a graph showing the effect of the eye drops of Example 2 [0.1% compound A] (a) and Example 5 [0.1% compound C] (b) on the optic disc blood flow kinetic, wherein the ordinate shows relative optic disc blood flow, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop and ○ shows control eye (n=6, * p<0.05, ** p<0.01, *** p<0.001 paired t-test).

Detailed Description of the Invention

55 [0012] In the present invention, glaucoma is exemplified by primary open angle glaucoma, normal pressure glaucoma, hypersecretion glaucoma, ocular hypertension, acute angle closure glaucoma, chronic angle closer glaucoma, plateau iris syndrome, combined-mechanism glaucoma, steroid glaucoma, capsular glaucoma, pigmentary glaucoma,

secondary glaucoma associated with amyloidosis, neovascular glaucoma, malignant glaucoma and the like.

[0013] In the present invention, Rho kinase means serine/threonine kinase activated along with the activation of Rho. For example, ROK α (ROCKII:Leung, T. et al, J. Biol. Chem., 270, 29051-29054, 1995), p160 ROCK (ROK β , ROCK-I :Ishizaki, T. et al, The EMBO J., 15(8), 1885-1893, 1996) and other proteins having a serine/threonine kinase activity are exemplified.

[0014] The compound having a Rho kinase inhibitory activity used as an active ingredient in the present invention may be any as long as it has a Rho kinase inhibitory activity. For example, the compounds of the formula (I) are exemplified. Of these, a compound of the formula (I') is more preferably used. In the present invention, a compound having one kind of Rho kinase inhibitory activity can be used alone or, where necessary, several kinds of the compounds can be used.

[0015] In the present specification, each symbol of the formulas (I) and (I') is defined as follows.

[0016] Alkyl at R, R' and R 1 is linear or branched alkyl having 1 to 10 carbon atoms, which is exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and the like, with preference given to alkyl having 1 to 4 carbon atoms.

[0017] Cycloalkyl at R, R' and R 1 has 3 to 7 carbon atoms and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

[0018] Cycloalkylalkyl at R, R' and R 1 is that wherein the cycloalkyl moiety is the above-mentioned cycloalkyl having 3 to 7 carbon atoms and the alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl and the like), which is exemplified by cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclopropylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, cyclopropylpropyl, cyclopentylpropyl, cyclohexylpropyl, cycloheptylpropyl, cyclopropylbutyl, cyclopentylbutyl, cyclohexylbutyl, cycloheptylbutyl, cyclopropylhexyl, cyclopentylhexyl, cyclohexylhexyl, cycloheptylhexyl and the like.

[0019] Aralkyl at R, R' and R 1 is that wherein alkyl moiety is alkyl having 1 to 4 carbon atoms and is exemplified by phenylalkyl such as benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl and the like.

[0020] The substituent of optionally substituted cycloalkyl, cycloalkylalkyl, phenyl and aralkyl on the ring at R, R' and R 1 is halogen (e.g., chlorine, bromine, fluorine and iodine), alkyl (same as alkyl at R, R' and R 1), alkoxy (linear or branched alkoxy having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, hexyloxy and the like), aralkyl (same as aralkyl at R, R' and R 1) or haloalkyl (alkyl at R, R' and R 1 which is substituted by 1-5 halogen, and exemplified by fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl and the like), nitro, amino, cyano, azide and the like.

[0021] The group formed by R and R' or R' and R 1 in combination together with the adjacent nitrogen atom, which forms a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom is preferably a 5 or 6-membered ring and bonded ring thereof. Examples thereof include 1-pyrrolidinyl, piperidino, 1-piperazinyl, morpholino, thiomorpholino, 1-imidazolyl, 2,3-dihydrothiazol-3-yl and the like. The substituent of the optionally substituted nitrogen atom is exemplified by alkyl, aralkyl, haloalkyl and the like. As used herein, alkyl, aralkyl and haloalkyl are as defined for R, R' and R 1 .

[0022] Alkyl at R 2 is as defined for R, R' and R 1 .

[0023] Halogen, alkyl, alkoxy and aralkyl at R 3 and R 4 are as defined for R, R' and R 1 .

[0024] Acyl at R 3 and R 4 is alkanoyl having 2 to 6 carbon atoms (e.g., acetyl, propionyl, butyryl, valeryl, pivaloyl and the like), benzoyl or phenylalkanoyl wherein the alkanoyl moiety has 2 to 4 carbon atoms (e.g., phenylacetyl, phenylpropionyl, phenylbutyryl and the like).

[0025] Alkylamino at R 3 and R 4 is that wherein the alkyl moiety is alkylamino having linear or branched alkyl having 1 to 6 carbon atoms. Examples thereof include methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, tert-butylamino, pentylamino, hexylamino and the like.

[0026] Acylamino at R 3 and R 4 is that wherein acyl moiety is alkanoyl having 2 to 6 carbon atoms, benzyl or the alkanoyl moiety is phenylalkanoyl having 2 to 4 carbon atoms and the like, which is exemplified by acetylamino, propionylamino, butyrylamino, valerylamino, pivaloylamino, benzoylamino, phenylacetylarnino, phenylpropionylamino, phenylbutyrylamino and the like.

[0027] Alkythio at R 3 and R 4 is that wherein the alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms, which is exemplified by methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, hexylthio and the like.

[0028] Aralkyloxy at R 3 and R 4 is that wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, which is exemplified by benzylxy, 1-phenylethoxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutyloxy and the like.

[0029] Aralkylthio at R 3 and R 4 is that wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, which is exemplified by benzylthio, 1-phenylethylthio, 2-phenylethylthio, 3-phenylpropylthio, 4-phenylbutylthio and the like.

[0030] Alkoxy carbonyl at R 3 and R 4 is that wherein the alkoxy moiety is linear or branched alkoxy having 1 to 6 carbon atoms, which is exemplified by methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl and the

like.

[0031] Alkylcarbamoyl at R³ and R⁴ is carbamoyl mono- or di-substituted by alkyl having 1 to 4 carbon atoms, which is exemplified by methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, propylcarbamoyl, dipropylcarbamoyl, butylcarbamoyl, dibutylcarbamoyl and the like.

5 [0032] Alkoxy at R⁵ is as defined for R, R' and R¹.

[0033] Alkoxy carbonyloxy at R⁵ is that wherein the alkoxy moiety is linear or branched alkoxy having 1 to 6 carbon atoms, which is exemplified by methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, sec-butoxycarbonyloxy, tert-butoxycarbonyloxy, pentyloxycarbonyloxy, hexyloxycarbonyloxy and the like.

10 [0034] Alkanoyloxy at R⁵ is that wherein the alkanoyl moiety is alkanoyl having 2 to 6 carbon atoms, which is exemplified by acetyloxy, propionyloxy, butyryloxy, valeryloxy, pivaloxy and the like.

[0035] Aralkyloxycarbonyloxy at R⁵ is that wherein the aralkyl moiety is aralkyl having C₁-C₄ alkyl, which is exemplified by benzoyloxycarbonyloxy, 1-phenylethoxy carbonyloxy, 2-phenylethoxy carbonyloxy, 3-phenylpropyloxycarbonyloxy, 4-phenylbutyloxycarbonyloxy and the like.

15 [0036] Alkyl at R⁶ is as defined for R, R' and R¹; alkyl at R⁸ and R⁹ is as defined for R, R' and R¹; and aralkyl at R⁸ and R⁹ is as defined for R, R' and R¹.

[0037] Alkyl at R⁷ is as defined for R, R' and R¹ and aralkyl at R⁷ is as defined for R, R' and R¹.

[0038] The group formed by R⁶ and R⁷ in combination, which forms a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom, is imidazol-2-yl, thiazol-2-yl, oxazol-2-yl, imidazolin-2-yl, 20 3,4,5,6-tetrahydropyridin-2-yl, 3,4,5,6-tetrahydropyrimidin-2-yl, 1,3-oxazolin-2-yl, 1,3-thiazolin-2-yl or optionally substituted benzimidazol-2-yl, benzothiazol-2-yl, benzoxazol-2-yl and the like having a substituent such as halogen, alkyl, alkoxy, haloalkyl, nitro, amino, phenyl, aralkyl and the like. As used herein, halogen, alkyl, alkoxy, haloalkyl and aralkyl are as defined for R, R' and R¹.

25 [0039] The substituent of the above-mentioned optionally substituted nitrogen atom is exemplified by alkyl, aralkyl, haloalkyl and the like. As used herein, alkyl, aralkyl and haloalkyl are as defined for R, R' and R¹.

[0040] Hydroxyalkyl at R¹⁰ and R¹¹ is linear or branched alkyl having 1 to 6 carbon atoms which is substituted by 1 to 3 hydroxy, which is exemplified by hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl and the like. Alkyl at R¹⁰ and R¹¹ is as defined for R, R' and R¹; haloalkyl and alkoxy carbonyl at R¹⁰ and R¹¹ are as defined for R, R' and R¹; aralkyl at R¹⁰ and R¹¹ is as defined for R, R' and R¹; and cycloalkyl formed by R¹⁰ and R¹¹ in combination is the same as cycloalkyl at R, R' and R¹.

[0041] Alkyl at L is as defined for R, R' and R¹.

[0042] Aminoalkyl at L is a linear or branched alkyl having 1 to 6 carbon atoms, which is substituted by amino, which is exemplified by aminomethyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, 6-aminohexyl and the like.

35 [0043] Mono- or dialkylaminoalkyl at L is mono- or di-substituted aminoalkyl with alkyl having 1 to 4 carbon atoms, which is exemplified by methylaminomethyl, dimethylaminomethyl, ethylaminomethyl, diethylaminomethyl, propylaminomethyl, dipropylaminomethyl, butylaminomethyl, dibutylaminomethyl, 2-dimethylaminoethyl, 2-diethylaminoethyl and the like.

[0044] Carbamoylalkyl at L is linear or branched alkyl having 1 to 6 carbon atoms substituted by carbamoyl, which 40 is exemplified by carbamoylmethyl, 2-carbamoylethyl, 1-carbamoylethyl, 3-carbamoylpropyl, 4-carbamoylbutyl, 5-carbamoylpentyl, 6-carbamoylhexyl and the like.

[0045] Phthalimidoalkyl at L is linear or branched alkyl having 1 to 6 carbon atoms, which is substituted by phthalimide. Examples thereof include phthalimidomethyl, 2-phthalimidoethyl, 1-phthalimidoethyl, 3-phthalimidopropyl, 4-phthalimidobutyl, 5-phthalimidopentyl, 6-phthalimidohexyl and the like.

45 [0046] Alkyl at B is as defined for R, R' and R¹.

[0047] Alkoxy at B is as defined for R, R' and R¹.

[0048] Aralkyl at B is as defined for R, R' and R¹.

[0049] Aralkyloxy at B is as defined for R³ and R⁴.

[0050] Aminoalkyl at B is as defined for L.

50 [0051] Hydroxyalkyl at B is as defined for R¹⁰ and R¹¹.

[0052] Alkanoyloxyalkyl at B is that wherein linear or branched alkyl having 1 to 6 carbon atoms is substituted by alkanoyloxy having alkanoyl moiety having 2 to 6 carbon atoms, which is exemplified by acetyloxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, acetoxyethyl, propionyloxyethyl, butyryloxyethyl, valeryloxyethyl, pivaloyloxyethyl and the like.

55 [0053] Alkoxy carbonylalkyl at B is that wherein linear or branched alkyl having 1 to 6 carbon atoms is substituted by alkoxy carbonyl having alkoxy moiety having 1 to 6 carbon atoms, which is exemplified by methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, isopropoxycarbonylmethyl, butoxycarbonylmethyl, isobutoxycarbonylmethyl, sec-butoxycarbonylmethyl, tert-butoxycarbonylmethyl, pentyloxycarbonylmethyl, hexyloxycarbonylmethyl,

methoxycarbonylethyl, ethoxycarbonylethyl, propoxycarbonylethyl, isopropoxycarbonylethyl, butoxycarbonylethyl, isobutoxycarbonylethyl, sec-butoxycarbonylethyl, tert-butoxycarbonylethyl, pentyloxycarbonylethyl, hexyloxycarbonylethyl and the like.

[0054] Halogen at Q¹, Q² and Q³ is as defined for R, R' and R¹.

5 [0055] Aralkyloxy at Q¹ and Q² is as defined for R³ and R⁴.

[0056] Alkoxy at Q³ is as defined for R, R' and R¹.

[0057] Alkylene at W, X and Y is linear or branched alkylene having 1 to 6 carbon atoms, which is exemplified by methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene and the like.

10 [0058] Alkenylene at Y is linear or branched alkenylene having 2 to 6 carbon atoms, which is exemplified by vinylene, propylene, butenylene, pentenylene and the like.

[0059] Alkyl at Rb is as defined for R, R' and R¹.

[0060] Aralkyl at Rb is as defined for R, R' and R¹.

[0061] Aminoalkyl at Rb is as defined for L.

[0062] Mono- or dialkylaminoalkyl at Rb is as defined for L.

15 [0063] The heterocycle when single ring containing nitrogen at Rc is pyridine, pyrimidine, pyridazine, triazine, pyrazole, triazole and the like, and when it is a condensed ring, it is exemplified by pyrrolopyridine (e.g., 1H-pyrrolo[2,3-b]pyridine, 1H-pyrrolo[3,2-b]pyridine, 1H-pyrrolo[3,4-b]pyridine and the like), pyrazolopyridine (e.g., 1H-pyrazolo[3,4-b]pyridine, 1H-pyrazolo[4,3-b]pyridine and the like), imidazopyridine (e.g., 1H-imidazo[4,5-b]pyridine and the like), pyrrolopyrimidine (e.g., 1H-pyrrolo[2,3-d]pyrimidine, 1H-pyrrolo[3,2-d]pyrimidine, 1H-pyrrolo[3,4-d]pyrimidine and the like),

20 pyrazolopyrimidine (e.g., 1H-pyrazolo[3,4-d]pyrimidine, pyrazolo[1,5-a]pyrimidine, 1H-pyrazolo[4,3-d]pyrimidine and the like), imidazopyrimidine (e.g., imidazo[1,2-a]pyrimidine, 1H-imidazo[4,5-d]pyrimidine and the like), pyrrolotriazine (e.g., pyrrolo[1,2-a]-1,3,5-triazine, pyrrolo[2,1-f]-1,2,4-triazine), pyrazolotriazine (e.g., pyrazolo[1,5-a]-1,3,5-triazine and the like), triazolopyridine (e.g., 1H-1,2,3-triazolo[4,5-b]pyridine and the like), triazolopyrimidine (e.g., 1,2,4-triazolo[1,5-a]pyrimidine, 1,2,4-triazolo[4,3-a]pyrimidine, 1H-1,2,3-triazolo[4,5-d]pyrimidine and the like), cinnoline, quinazoline, quinoline, pyridopyridazine (e.g., pyrido[2,3-c]pyridazine and the like), pyridopyrazine (e.g., pyrano[2,3-b]pyrazine and the like), pyridopyrimidine (e.g., pyrido[2,3-d]pyrimidine, pyrido[3,2-d]pyrimidine and the like), pyrimidopyrimidine (e.g., pyrimido[4,5-d]pyrimidine, pyrimido[5,4-d]pyrimidine and the like), pyrazinopyrimidine (e.g., pyrazino[2,3-d]pyrimidine and the like), naphthyridine (e.g., 1,8-naphthyridine and the like), tetrazolopyrimidine (e.g., tetrazolo[1,5-a]pyrimidine and the like), thienopyridine (e.g., thieno[2,3-b]pyridine and the like), thienopyrimidine (e.g., thieno[2,3-d]pyrimidine and the like),

25 thiazolopyridine (e.g., thiazolo[4,5-b]pyridine, thiazolo[5,4-b]pyridine and the like), thiazolopyrimidine (e.g., thiazolo[4,5-d]pyrimidine, thiazolo[5,4-d]pyrimidine and the like), oxazolopyridine (e.g., oxazolo[4,5-b]pyridine, oxazolo[5,4-b]pyridine and the like), oxazolopyrimidine (e.g., oxazolo[4,5-d]pyrimidine, oxazolo[5,4-d]pyrimidine and the like), furopyridine (e.g., furo[2,3-b]pyridine, furo[3,2-b]pyridine and the like), furopyrimidine (e.g., furo[2,3-d]pyrimidine, furo[3,2-d]pyrimidine and the like), 2,3-dihydropyrrolopyridine (e.g., 2,3-dihydro-1H-pyrrolo[2,3-b]pyridine, 2,3-dihydro-1H-pyrrolo[3,2-b]pyridine and the like), 2,3-dihydropyrrolopyrimidine (e.g., 2,3-dihydro-1H-pyrrolo[2,3-d]pyrimidine, 2,3-dihydro-1H-pyrrolo[3,2-d]pyrimidine and the like), 5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine, 5,6,7,8-tetrahydro-1,8-naphthyridine, 5,6,7,8-tetrahydroquinoline and the like. When these rings form a hydrogenated aromatic ring, the carbon atom in the ring may be carbonyl and includes, for example, 2,3-dihydro-2-oxopyrrolopyridine, 2,3-dihydro-2,3-dioxopyrrolopyridine, 7,8-dihydro-7-oxo-1,8-naphthyridine, 5,6,7,8-tetrahydro-7-oxo-1,8-naphthyridine and the like, with preference given to pyridin and pyrrolopyridine.

30 [0064] These rings may be substituted by a substituent such as halogen, alkyl, alkoxy, aralkyl, haloalkyl, nitro, amino, alkylamino, cyano, formyl, acyl, aminoalkyl, mono- or dialkylaminoalkyl, azide, carboxy, alkoxy carbonyl, carbamoyl, alkylcarbamoyl, alkoxycarbonyl (e.g., methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl and the like), optionally substituted hydrazino and the like.

35 [0065] As used herein, the substituent of the optionally substituted hydrazino includes alkyl, aralkyl, nitro, cyano and the like, wherein alkyl and aralkyl are as defined for R, R' and R¹ and exemplified by methylhydrazino, ethylhydrazino, benzylhydrazino and the like.

40 [0066] The compound of the formula (I) [inclusive of the compounds of the formula (I')] is exemplified by the following compounds.

45

(1) 4-(2-pyridylcarbamoyl)piperidine

(2) 1-benzyloxycarbonyl-4-(4-pyridylcarbamoyl)piperidine

(3) 1-berizoyl-4-(4-pyridylcarbamoyl)piperidine

(4) 1-propyl-4-(4-pyridylcarbamoyl)piperidine

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(5) [3-(2-(2-thienylmethyl)phenoxy)-2-hydroxypropyl]-4-(4-pyridylcarbamoyl)piperidine

(6) 4-(4-pyridylcarbamoyl)piperidine

(7) 1-benzyl-4-(4-pyridylcarbamoyl)-1,2,5,6-tetrahydropyridine

(8) 3-(4-pyridylcarbamoyl)piperidine

(9) 1-benzyl-3-(4-pyridylcarbamoyl)piperidine
 (10) 1-(2-(4-benzyloxyphenoxy)ethyl)-4-(N-(2-pyridyl)-N-benzylcarbamoyl)pyridine
 (11) 1-formyl-4-(4-pyridylcarbamoyl)piperidine
 (12) 4-(3-pyridylcarbamoyl)piperidine
 5 (13) 1-isopropyl-4-(4-pyridylcarbamoyl)piperidine
 (14) 1-methyl-4-(4-pyridylcarbamoyl)piperidine
 (15) 1-hexyl-4-(4-pyridylcarbamoyl)piperidine
 (16) 1-benzyl-4-(4-pyridylcarbamoyl)piperidine
 (17) 1-(2-phenylethyl)-4-(4-pyridylcarbamoyl)piperidine
 10 (18) 1-(2-(4-methoxyphenyl)ethyl)-4-(4-pyridylcarbamoyl)piperidine
 (19) 1-(2-(4-methoxyphenyl)ethyl)-4-(2-pyridylcarbamoyl)piperidine
 (20) 1-(2-(4-chlorophenyl)ethyl)-4-(4-pyridylcarbamoyl)piperidine
 (21) 1-diphenylmethyl-4-(2-pyridylcarbamoyl)piperidine
 15 (22) 1-[2-(4-(5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)phenyl)ethyl]-4-(2-pyridylcarbamoyl)piperidine
 (23) 1-(4-(4,5-dihydro-2-furyl)phenyl)-4-(4-pyridylcarbamoyl)piperidine
 (24) 1-(2-nitrophenyl)-4-(4-pyridylcarbamoyl)piperidine
 (25) 1-(2-aminophenyl)-4-(4-pyridylcarbamoyl)piperidine
 (26) 1-nicotinoyl-4-(4-pyridylcarbamoyl)piperidine
 20 (27) 1-isonicotinoyl-4-(4-pyridylcarbamoyl)piperidine
 (28) 1-(3,4,5-trimethoxybenzoyl)-4-(4-pyridylcarbamoyl)piperidine
 (29) 1-acetyl-4-(4-pyridylcarbamoyl)piperidine
 (30) 1-(3-(4-fluorobenzoyl)propyl)-4-(4-pyridylcarbamoyl)piperidine
 (31) 1-(3-(4-fluorobenzoyl)propyl)-4-(2-pyridylcarbamoyl)piperidine
 25 (32) 1-(1-(4-hydroxybenzoyl)ethyl)-4-(2-pyridylcarbamoyl)piperidine
 (33) 1-(1-(4-benzyloxybenzoyl)ethyl)-4-(2-pyridylcarbamoyl)piperidine
 (34) 1-(2-(4-hydroxyphenoxy)ethyl)-4-(2-pyridylcarbamoyl)piperidine
 (35) 1-(4-(4-fluorophenyl)-4-hydroxybutyl)-4-(4-pyridylcarbamoyl)piperidine
 (36) 1-(1-methyl-2-(4-hydroxyphenyl)-2-hydroxyethyl)-4-(2-pyridylcarbamoyl)piperidine
 (37) 1-cinnamyl-4-(2-pyridylcarbamoyl)piperidine
 30 (38) 1-(2-hydroxy-3-phenoxypropyl)-4-(4-pyridylcarbamoyl)piperidine
 (39) 1-(2-hydroxy-3-phenoxypropyl)-4-(3-pyridylcarbamoyl)piperidine
 (40) 1-(2-hydroxy-3-phenoxypropyl)-4-(2-pyridylcarbamoyl)piperidine
 (41) 1-(2-phenylethyl)-4-[N-(2-pyridyl)-N-(2-(N,N-dimethylamino)ethyl)carbamoyl]piperidine
 (42) 1-benzyloxycarbonyl-4-(2-pyridylcarbamoyl)piperidine
 35 (43) 1-(3-chlorophenyl)carbamoyl-4-(4-pyridylcarbamoyl)piperidine
 (44) 1-[N-(2-pyridyl)-N-(2-(N,N-dimethylamino)ethyl)carbamoyl]piperidine
 (45) 1-methyl-4-(4-pyridylcarbamoyl)-1,2,5,6-tetrahydropyridine
 (46) 1-nicotinoyl-3-(4-pyridylcarbamoyl)piperidine
 (47) 1-[2-(4-fluorobenzoyl)ethyl]-4-(4-pyridylcarbamoyl)piperidine
 40 (48) 1-(6-chloro-2-methylimidazo[1,2-a]pyridine-3-carbonyl)-4-(4-pyridylcarbamoyl)piperidine
 (49) 1-(4-nitrobenzyl)-4-(4-pyridylcarbamoyl)piperidine
 (50) 1-hexyl-4-(4-pyridylcarbamoyl)piperidine
 (51) 1-benzyloxycarbonyl-4-(2-chloro-4-pyridylcarbamoyl)piperidine
 45 (52) 4-(2-chloro-4-pyridylcarbamoyl)piperidine
 (53) 1-(2-chloronicotinoyl)-4-(4-pyridylcarbamoyl)piperidine
 (54) 3-(2-chloro-4-pyridylcarbamoyl)piperidine
 (55) 1-(4-phthalimidobutyl)-4-(4-pyridylcarbamoyl)piperidine
 (56) 1-(3,5-di-tert-butyl-4-hydroxycinnamoyl)-4-(4-pyridylcarbamoyl)piperidine
 (57) 1-carbamoylmethyl-4-(4-pyridylcarbamoyl)piperidine
 50 (58) 1-benzyloxycarbonyl-4-(5-nitro-2-pyridylcarbamoyl)piperidine
 (59) 4-(5-nitro-2-pyridylcarbamoyl)piperidine
 (60) trans-4-benzyloxycarboxamidomethyl-1-(4-pyridylcarbamoyl)cyclohexane
 (61) trans-4-aminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
 55 (62) trans-4-formamidomethyl-1-(4-pyridylcarbamoyl)cyclohexane
 (63) trans-4-dimethylaminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
 (64) N-benzylidene-trans-(4-pyridylcarbamoyl)cyclohexylmethylamine
 (65) trans-4-benzylaminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
 (66) trans-4-isopropylaminomethyl-1-(4-pyridylcarbamoyl)cyclohexane

(67) trans-4-nicotinoylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
 (68) trans-4-cyclohexylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
 (69) trans-4-benzylloxycarboxamide-1-(4-pyridylcarbamoyl)-cyclohexane
 (70) trans-4-amino-1-(4-pyridylcarbamoyl)cyclohexane
 5 (71) trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (72) trans-4-aminomethyl-cis-2-methyl-1-(4-pyridylcarbamoyl)-cyclohexane
 (73) (+)-trans-4-(1-benzylloxycarboxamidopropyl)-1-cyclohexanecarboxylic acid
 (74) (+)-trans-4-(1-benzylloxycarboxamidopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (75) (-)-trans-4-(1-benzylloxycarboxamidopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
 10 (76) (+)-trans-4-(1-aminopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (77) (-)-trans-4-(1-aminopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (78) (-)-trans-4-(1-benzylloxycarboxamidoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (79) (+)-trans-4-(1-benzylloxycarboxamidoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (80) (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
 15 (81) (-)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (82) trans-4-(4-chlorobenzoyl)aminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
 (83) trans-4-aminomethyl-1-(2-pyridylcarbamoyl)cyclohexane
 (84) trans-4-benzylloxycarboxamidomethyl-1-(2-pyridylcarbamoyl)-cyclohexane
 20 (85) trans-4-methylaminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
 (86) trans-4-(N-benzyl-N-methylamino)methyl-1-(4-pyridylcarbamoyl)cyclohexane
 (87) trans-4-aminomethyl-1-(3-pyridylcarbamoyl)cyclohexane
 (88) trans-4-aminomethyl-1-[(3-hydroxy-2-pyridyl)carbamoyl]-cyclohexane
 (89) trans-4-benzylloxycarboxamidomethyl-1-(3-pyridylcarbamoyl)-cyclohexane
 (90) trans-4-benzylloxycarboxamidomethyl-1-[(3-benzyloxy-2-pyridyl)carbamoyl]-cyclohexane
 25 (91) trans-4-phthalimidomethyl-1-(4-pyridylcarbamoyl)cyclohexane
 (92) trans-4-benzylloxycarboxamidomethyl-1-(3-methyl-4-pyridylcarbamoyl)cyclohexane
 (93) trans-4-aminomethyl-1-(3-methyl-4-pyridylcarbamoyl)-cyclohexane
 (94) 4-(trans-4-benzylloxycarboxamidomethylcyclohexylcarbonyl)amino-2,6-dimethylpyridine-N-oxide
 (95) 4-(trans-4-aminomethylcyclohexylcarbonyl)amino-2,6-dimethylpyridine-N-oxide
 30 (96) trans-4-aminomethyl-1-(2-methyl-4-pyridylcarbamoyl)-cyclohexane
 (97) trans-4-(1-benzylloxycarboxamidoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (98) trans-4-(1-amino-1-methylethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
 (99) trans-4-(2-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (100) trans-4-(2-amino-1-methylethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
 35 (101) trans-4-(1-aminopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (102) trans-4-aminomethyl-trans-1-methyl-1-(4-pyridylcarbamoyl)-cyclohexane
 (103) trans-4-benzylaminomethyl-cis-2-methyl-1-(4-pyridylcarbamoyl)cyclohexane
 (104) trans-4-(1-benzylloxycarboxamide-1-methylethyl)-1-(4-pyridylcarbamoyl)cyclohexane
 (105) trans-4-benzylloxycarboxamidomethyl-1-(N-methyl-4-pyridylcarbamoyl)cyclohexane
 40 (106) trans-4-(1-acetamide-1-methylethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
 (107) trans-N-(6-amino-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
 (108) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
 (109) (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
 (110) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
 45 (111) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
 (112) (+)-trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
 (113) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
 (114) (+)-trans-N-(2-amino-4-pyridyl)-4-(1-aminoethyl)cyclohexanecarboxamide
 (115) trans-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-aminomethylcyclohexanecarboxamide
 50 (116) (+)-trans-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
 (117) trans-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
 (118) trans-N-(4-pyrimidinyl)-4-aminomethylcyclohexanecarboxamide
 (119) trans-N-(3-amino-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
 (120) trans-N-(7H-imidazo[4,5-d]pyrimidin-6-yl)-4-aminomethylcyclohexanecarboxamide
 55 (121) trans-N-(3H-1,2,3-triazolo[4,5-d]pyrimidin-7-yl)-4-aminomethylcyclohexanecarboxamide
 (122) trans-N-(1-benzyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
 (123) trans-N-(1H-5-pyrazolyl)-4-aminomethylcyclohexanecarboxamide
 (124) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide

(125) trans-N-(4-pyridazinyl)-4-aminomethylcyclohexanecarboxamide
 (126) trans-N-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-aminomethylcyclohexanecarboxamide
 (127) trans-N-(2-amino-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
 (128) trans-N-(thieno[2,3-d]pyrimidin-4-yl)-4-aminomethylcyclohexanecarboxamide
 5 (129) trans-N-(5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7-yl)-4-aminomethylcyclohexanecarboxamide
 (130) trans-N-(3-cyano-5-methylpyrazolo[1,5-a]pyrimidin-7-yl)-4-aminomethylcyclohexanecarboxamide
 (131) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
 (132) trans-N-(2-(1-pyrrolidinyl)-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
 10 (133) trans-N-(2,6-diamino-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
 (134) (+)-trans-N-(7-methyl-1,8-naphthyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
 (135) trans-N-(1-benzylloxymethyl)pyrrolo[2,3-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
 (136) (+)-trans-N-(1-methylpyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
 (137) trans-N-benzyl-N-(2-benzylamino-4-pyridyl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
 15 (138) trans-N-(2-azide-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
 (139) trans-N-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
 (140) trans-N-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
 (141-1) trans-N-(2-carboxy-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
 20 (141-2) (R)-(+)-trans-N-(3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
 (142) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-guanidinomethylcyclohexanecarboxamide
 (143) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethylcyclohexanecarboxamide
 25 (144) trans-N-(4-pyridyl)-4-guanidinomethylcyclohexanecarboxamide
 (145) trans-N-(1-methylpyrrolo[2,3-b]pyridin-4-yl)-4-(guanidinomethyl)cyclohexanecarboxamide
 (146) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(2-imidazolin-2-yl)aminomethylcyclohexanecarboxamide
 (147) trans-N-(1-benzylloxymethyl)pyrrolo[2,3-b]pyridin-4-yl)-4-guanidinomethylcyclohexanecarboxamide
 30 (148) trans-N-(2-amino-4-pyridyl)-4-guanidinomethylcyclohexanecarboxamide
 (149) trans-N-(1-benzylloxymethyl)1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(2-imidazolin-2-yl)aminomethylcyclohexanecarboxamide
 (150) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-benzylguanidinomethyl)-cyclohexanecarboxamide
 (151) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-phenylguanidinomethyl)-cyclohexanecarboxamide
 35 (152) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-propylguanidinomethyl)-cyclohexanecarboxamide
 (153) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-octylguanidinomethyl)-cyclohexanecarboxamide
 (154) trans-N-(1-benzylloxymethyl)pyrrolo[2,3-b]pyridin-4-yl)-4-(2-benzyl-3-ethylguanidinomethyl)cyclohexanecarboxamide
 40 (155) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(imidazol-2-yl)aminomethylcyclohexanecarboxamide
 (156) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(thiazol-2-yl)aminomethylcyclohexanecarboxamide
 (157) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide
 (158) N-(4-pyridyl)-4-(1-amino-1-methylethyl)benzamide
 45 (159) N-(4-pyridyl)-4-aminomethyl-2-benzylbenzamide
 (160) N-(4-pyridyl)-4-aminomethyl-2-ethoxybenzamide
 (161) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-nitrobenzamide
 (162) (R)-(-)-N-(4-pyridyl)-3-amino-4-(1-aminoethyl)benzamide
 (163) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-chlorobenzamide
 50 (164) N-(4-pyridyl)-3-aminomethylbenzamide
 (165) (R)-(-)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide
 (166) (R)-(-)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide
 (167) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethylbenzamide
 (168) N-(4-pyridyl)-4-guanidinomethylbenzamide
 (169) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-fluorobenzamide
 55 (170) N-(4-pyridyl)-4-aminomethylbenzamide
 (171) N-(4-pyridyl)-4-aminomethyl-2-hydroxybenzamide
 (172) N-(4-pyridyl)-4-(2-aminoethyl)benzamide
 (173) N-(4-pyridyl)-4-aminomethyl-3-nitrobenzamide
 (174) N-(4-pyridyl)-3-amino-4-aminomethylbenzamide
 (175) (S)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide
 60 (176) (S)-(-)-N-(4-pyridyl)-2-(1-aminoethyl)benzamide
 (177) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-2-chlorobenzamide
 (178) (R)-(-)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-(3-propylguanidino)ethyl)benzamide
 (179) (R)-(-)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)-3-azidebenzamide

- (180) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)-2-nitrobenzamide
- (181) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-ethoxybenzamide
- (182) (R)-(+)-N-(3-iodo-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide
- (183) (R)-(+)-N-(3-iodo-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)-3-azidebenzamide
- 5 (184) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-hydroxybenzamide
- (185) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethyl-3-nitrobenzamide
- (186) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-guanidinoethyl)-3-nitrobenzamide
- (187) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)-2-nitrobenzamide
- 10 (188) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinobenzamide
- (189) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)-3-nitrobenzamide
- (190) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-guanidinoethyl)benzamide
- (191) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino-2-hydroxyethyl)benzamide
- (192) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethyl-3-nitrobenzamide
- 15 (193) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-piperidinecarboxamide
- (194) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-piperidinecarboxamide
- (195) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1-aminoacetyl-4-piperidinecarboxamide
- (196) N-(1-methoxymethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-4-piperidinecarboxamide
- (197) N-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-piperidinecarboxamide
- 20 (198) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(2-phenylethyl)-4-piperidinecarboxamide
- (199) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-amidino-4-piperidinecarboxamide
- (200) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(3-phenylpropyl)-4-piperidinecarboxamide
- (201) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-benzyl-4-piperidinecarboxamide
- 25 (202) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1-(2-phenylethyl)-4-piperidinecarboxamide
- (203) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1-(3-phenylpropyl)-4-piperidinecarboxamide

25 [0067] Preferred are compounds (80), (109), (110), (112), (115), (142), (143), (144), (145), (153), (157), (163), (165), (166) and (179).

30 [0068] The compound having a Rho kinase inhibitory activity may be a pharmaceutically acceptable acid addition salt, wherein the acid is exemplified by inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and the like, and organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, tartaric acid, salicylic acid and the like. A compound having a carboxylic group can be converted to a salt with a metal such as sodium, potassium, calcium, magnesium, aluminum and the like, a salt with an amino acid such as lysine and the like. Further, monohydrate, dihydrate, 1/2 hydrate, 1/3 hydrate, 2/3 hydrate, 3/2 hydrate, 6/5 hydrate and the like are encompassed in the present invention.

35 [0069] The compound of the formula (I) can be synthesized by a method described in, for example, JP-A-62-89679, JP-A-3-218356, JP-A-5-194401, JP-A-6-41080, WO95/28387, WO98/06433 and the like.

40 [0070] When the above-mentioned compound having a Rho kinase inhibitory activity has an optical isomer, its racemate or cis-trans isomers, all of them can be used in the present invention. These isomers can be isolated by a conventional method or can be produced using starting materials of the isomers.

45 [0071] A compound having a Rho kinase inhibitory activity, particularly, a compound of the formula (I), an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof have intraocular pressure lowering action, optic disc blood flow improving action and aqueous outflow promoting action in mammals inclusive of human, cow, horse, dog, mouse, rat and the like. Therefore, they can be used as an agent for the prophylaxis and treatment of various types of glaucoma, such as primary open angle glaucoma, normal pressure glaucoma, hypersecretion glaucoma, ocular hypertension, acute angle closure glaucoma, chronic angle closer glaucoma, plateau iris syndrome, combined-mechanism glaucoma, steroid glaucoma, capsular glaucoma, pigmentary glaucoma, secondary glaucoma associated with amyloidosis, neovascular glaucoma, malignant glaucoma and the like.

50 [0072] The agent for the prophylaxis and treatment of glaucoma of the present invention is administered orally or parenterally. The dosage form may be, for example, oral preparation such as tablet, capsule, syrup and the like, or parenteral preparation such as liquid injection (e.g., solution, emulsion, suspension and the like), external agent [e.g., ointment (particularly eye ointment), eye drop and the like], and the like. In consideration of the influence and effect on other circulatory systems, the dosage form of administration to local site in the eye is preferable. The dosage form of eye drop or eye ointment is particularly preferable.

55 [0073] A preparation having the aforementioned dosage form can be prepared by mixing the inventive compound with an additive necessary for formulating a preparation, such as typical carrier, excipient, binder, stabilizer and the like and by following a conventional method. For example, the compound having a Rho kinase inhibitory activity is mixed with a pharmaceutically acceptable carrier (e.g., excipient, binder, disintegrator, corrective, corrigent, emulsifier, diluent, solubilizer and the like) to give a pharmaceutical composition or a pharmaceutical preparation in the form of tablet, pill,

powder, granule, capsule, troche, syrup, liquid, emulsion, suspension, injection (e.g., liquid, suspension and the like), suppository, inhalant, percutaneous absorber, eye drop, eye ointment and the like in the form suitable for oral or parenteral preparation.

[0074] When preparing a solid preparation, additives such as sucrose, lactose, cellulose sugar, D-mannitol, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectines, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, calcium phosphate, sorbitol, glycine, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, glycerol, polyethyleneglycol, sodium hydrogencarbonate, magnesium stearate, talc and the like are used. Tablets can be applied with a typical coating, where necessary, to give sugar coated tablets, enteric tablets, film-coated tablets, two-layer tablets and multi-layer tablets.

[0075] When preparing a semi-solid preparation, animal and plant fats and oils (e.g., olive oil, corn oil, castor oil and the like), mineral fats and oils (e.g., petrolatum, white petrolatum, solid paraffin and the like), wax (e.g., jojoba oil, carnauba wax, bee wax and the like), partly or entirely synthesized glycerol fatty acid esters (e.g., lauric acid, myristic acid, palmitic acid and the like), and the like are used. Examples of commercially available products of these include Witepsol (manufactured by Dynamitnövel Ltd.), Farmazol (NOF Corporation) and the like.

[0076] When preparing a liquid preparation, an additive, such as sodium chloride, glucose, sorbitol, glycerol, olive oil, propylene glycol, ethyl alcohol and the like, is used.

[0077] The liquid preparation may be, for example, injection, eye drop and the like.

[0078] When preparing an injection, a sterile aqueous solution such as physiological saline, isotonic solution, oil (e.g., sesame oil and soybean oil) and the like are used. Where necessary, a suitable suspending agent such as sodium carboxymethylcellulose, nonionic surfactant, solubilizer (e.g., benzyl benzoate and benzyl alcohol), and the like can be concurrently used.

[0079] Moreover, when an eye drop is prepared, an aqueous liquid or solution is used, which is particularly a sterile injectable aqueous solution. The eye drop can appropriately contain various additives such as buffer, stabilizer, wetting agent, emulsifier, suspending agent, surfactant, isotonicity agent, preservative and thickener.

[0080] The buffer may be, for example, phosphate buffer, borate buffer, citrate buffer, tartrate buffer, acetate buffer, amino acid and the like.

[0081] The stabilizer may be, for example, sodium edetate, citric acid and the like.

[0082] The wetting agent may be, for example, glycerol and the like.

[0083] The emulsifier may be, for example, polyvinylpyrrolidone and the like.

[0084] The suspending agent may be, for example, hydroxypropylmethylcellulose, methylcellulose and the like.

[0085] The surfactant may be, for example, polysorbate 80, polyoxyethylene hydrogenated castor oil and the like.

[0086] The isotonicity agent may be, for example, saccharides such as sorbitol, glucose, mannitol and the like, polyhydric alcohols such as glycerol, propylene glycol and the like, salts such as sodium chloride and the like, and the like.

[0087] The preservative may be, for example, quaternary ammonium salt such as benzalkonium chloride, benzethonium chloride and the like, p-hydroxybenzoate such as methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate and the like, benzyl alcohol, phenethyl alcohol, sorbic acid and salts thereof, thimerosal, chlorobutanol and the like.

[0088] The thickener may be, for example, hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, salts thereof and the like.

[0089] When in use as an eye drop, pH is preferably adjusted generally to about 4 - 9, preferably about 6 - 8.5.

[0090] When the preparation is an eye ointment, an ointment base (e.g., petrolatum, lanolin, plastibase and the like), a preservative (e.g., benzalkonium chloride, p-hydroxybenzoate, chlorobutanol and the like), and the like are appropriately selected and used for production.

[0091] The agent for the prophylaxis and treatment of glaucoma of the present invention contains an active ingredient in a proportion of 0.0001 - 100 w/w%, suitably 0.001 - 50 w/w%, of the preparation. While the dose and administration frequency vary depending on symptom, age, body weight and administration form, when it is used as an eye drop for an adult, a preparation containing a compound having a Rho kinase inhibitory activity in a proportion of 0.0001 - 10 w/w%, preferably 0.001 - 1 w/w%, is administered several times a day, preferably 1 - 6 times a day, by several drops, preferably 1 - 3 drops, each time. When it is used as an eye ointment, a preparation containing this compound in a proportion of 0.0001 - 10 w/w%, preferably 0.001 - 1 w/w%, can be applied several times a day, preferably 1 - 6 times a day.

50 Examples

[0092] The present invention is explained in detail by referring to examples and experimental examples. The present invention is not limited in any way by these examples.

55 Example 1: eye drop 1

[0093] (+)-trans-4-(1-Aminoethyl)-1-(4-pyridylcarbamoyl)-cyclohexane 2HCl 1H₂O (hereinafter Compound A),

which is a compound having a Rho kinase inhibitory activity, was dissolved in distilled water for injection. The pH was adjusted to 7 with sodium hydroxide and an eye drop having the following composition was prepared.

5

| | |
|--------------------------------------|--------------------|
| Compound A | 0.5 g |
| Sodium dihydrogenphosphate 2 hydrate | 0.1 g |
| Sodium chloride | 0.9 g |
| distilled water for injection | appropriate amount |
| Total amount | 100 ml |

10

15 **Example 2: eye drop 2**

[0094] In the same manner as in Example 1, an eye drop containing Compound A at a concentration of 0.1% was prepared.

20 **Example 3: eye drop 3**

[0095] In the same manner as in Example 1, an eye drop containing Compound A at a concentration of 0.03% was prepared.

25 **Example 4: eye drop 4**

[0096] In the same manner as in Example 1, an eye drop containing (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide 2HCl 6/5H₂O (hereinafter Compound B), which is a compound having a Rho kinase inhibitory activity, at a concentration of 0.03% was prepared.

30

Example 5: eye drop 5

[0097] In the same manner as in Example 1, an eye drop containing (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide 2HCl (hereinafter Compound C), which is a compound having a Rho kinase inhibitory activity, at a concentration of 0.1% was prepared.

Example 6: eye drop 6

[0098] In the same manner as in Example 5, an eye drop containing Compound C at a concentration of 0.03% was prepared.

Example 7: eye drop 7

[0099] In the same manner as in Example 1, an eye drop containing (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide 2HCl 1H₂O (hereinafter Compound D), which is a compound having a Rho kinase inhibitory activity, at a concentration of 0.03% was prepared.

Example 8: tablets

50 [0100] The Compound A, lactose, corn starch and crystalline cellulose were mixed, kneaded with polyvinylpyrrolidone K30 paste solution and passed through a 20-mesh sieve for granulation. After drying at 50°C for 2 hours, the granules were passed through a 24-mesh sieve, and talc and magnesium stearate were added. Using a ϕ 7 mm punch, tablets weighing 120 mg per tablet were prepared.

55

| | |
|------------|---------|
| Compound A | 10.0 mg |
|------------|---------|

(continued)

| | | |
|----|--------------------------|----------|
| 5 | Lactose | 50.0 mg |
| 10 | Corn starch | 20.0 mg |
| | Crystalline cellulose | 29.7 mg |
| | Polyvinylpyrrolidone K30 | 5.0 mg |
| | Talc | 5.0 mg |
| | Magnesium stearate | 0.3 mg |
| | | 120.0 mg |

Formulation Example 9: Capsules

[0101] The Compound A, lactose and corn starch were mixed, kneaded with polyvinylpyrrolidone K30 paste solution and passed through a 20-mesh sieve for granulation. After drying at 50°C for 2 hours, the granules were passed through a 24-mesh sieve and talc and magnesium stearate were added. The mixture was filled in hard capsules (No. 4) to give capsules weighing 120 mg.

| | | |
|----|--------------------------|----------|
| 20 | Compound A | 10.0 mg |
| 25 | Lactose | 70.0 mg |
| 30 | Corn starch | 35.0 mg |
| | Polyvinylpyrrolidone K30 | 2.0 mg |
| | Talc | 2.7 mg |
| | Magnesium stearate | 0.3 mg |
| | | 120.0 mg |

35 Experimental Example 1: effect on normal intraocular pressure of coloured rabbitExperiment method

[0102] Male Dutch coloured rabbits (body weight about 2 kg) were used. The rabbits were placed in a holding box for 3-5 hr a day for acclimation from one week prior to the test. The rabbits that showed steady intraocular pressure as measured by a tonometer [pneumatonomograph (manufactured by Alcon Lab. Inc.)] were selected and used for the test. After measurement of the initial value of the intraocular pressure, the eye drop (50 µl) of Example 1 was instilled into one eye, and a base, which was the eye drop of Example 1 except Compound A, was instilled into the other eye in the same manner and taken as the control eye. The intraocular pressure was measured with time at 30, 60, 90 and 120 min after instillation and thereafter at 60 min intervals until the intraocular pressure returned to the initial value, and the duration of the effect was examined.

Experiment result

[0103] The effect of the eye drop of Example 1 on the normal intraocular pressure is shown in Fig. 1. When compared to the control eye at 60 min after instillation, the maximum significant intraocular pressure lowering action of 5 mmHg was observed. For 180 min after instillation, a significant intraocular pressure lowering action as compared to the control eye was found. At 360 min after instillation, the intraocular pressure was almost the same as in the control eye and returned to the initial value.

Experimental Example 2: effect on blood flow of normal optic disc of coloured rabbit**Experiment method**

5 [0104] Male Dutch coloured rabbits (body weight about 2 kg) were used. The eye drop (50 μ l) of Example 1 was instilled into one eye, and a base, which was the eye drop of Example 1 except Compound A, was instilled into the other eye in the same manner and taken as the control eye. Using a laser speckle microcirculation analyzer, the blood flow of optic disc was measured at 30, 60, 90 and 120 min after instillation and thereafter at 60 min intervals till 300 min after the instillation.

10 [0105] **Experiment result**

15 [0105] The effect of the eye drop of Example 1 on the optic disc blood flow kinetic is shown in Fig. 2. When compared to the control eye, a 11% blood flow increasing action was found at 30 min after instillation, and a 15% significant blood flow increasing action was found at 60 min after instillation. The blood flow increased most (18%) at 120 min after instillation. The effect gradually decreased thereafter, but a significant blood flow increasing action was observed for 180 min after the instillation as compared to the control eye.

Experimental Example 3: effect on carbachol contraction of extracted ciliary muscle of white rabbit**Experiment method**

20 [0106] Male Japanese white rabbits (body weight about 2 kg) were euthanized by intravenous administration of an excess pentobarbital sodium. The eyeball was enucleated immediately thereafter and preserved in a Krebs solution (NaCl:112 mM, KCl:5.9 mM, CaCl₂ 2H₂O:2.0 mM, MgCl₂ 6H₂O:1.2 mM, NaH₂PO₄ 2H₂O:1.2 mM, NaHCO₃ 25 mM, Glucose:11.5 mM). The ciliary body separated from the eyeball was hung in a Magnus bath filled with the Krebs solution and equilibrated under a 20 - 30 mg resting tension. The changes in the tension of the preparation was measured with a transducer and recorded on a pen recorder via an amplifier. As the contraction drug, carbachol was used, and the inhibitory action on the dose dependent response of phasic contraction was studied. The test drug was (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane 2HCl 1H₂O (Compound A), which was added to the Magnus bath 5 min before addition of carbachol.

Experiment result

25 [0107] The effect of Compound A on the carbachol contraction is shown in Fig. 3. The ciliary muscle showed a dose dependent contraction by 10^{-6} - 3×10^{-4} M carbachol and Compound A showed non-competitive antagonism against carbachol contraction. The IC₅₀ of Compound A against carbachol contraction was 2.8×10^{-6} M.

30 [0108] The contraction and relaxation of the ciliary muscle play an important role in aqueous outflow. By the relaxation of the ciliary muscle, the aqueous outflow via trabecular meshwork can be inhibited but that via uveosclera is promoted (Takeshi Yoshitomi, Neuroophthalmol. Jpn., 15(1), 76-81, 1998). The relaxation of the ciliary muscle that promotes aqueous outflow is considered to result in lowering of the intraocular pressure.

35 [0109] In general, 1/1000 of eye drop is said to be transferred into anterior chamber (Kouji Honda: Practical Ophthalmology, Guide of ophthalmic drug, Bunkodo Co. Ltd., Tokyo, 387-392, 1994). When 0.5% Compound A is instilled by 50 μ l, 1/1000 thereof to be transferred into the anterior chamber is calculated to be 1.5×10^{-5} . Therefore, these test results are considered to show the concentration sufficiently effective in vivo as well.

Experimental Example 4: effect on normal intraocular pressure of white rabbits**Test drug**

40 [0110]

45 Compound A (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane 2HCl 1H₂O
 Compound B (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide 2HCl 6/5H₂O
 Compound C (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide 2HCl
 Compound D (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide 2HCl 1H₂O

50 [0111] In this experiment, 0.1% eye drop and 0.03% eye drop containing Compound A (each prepared in Example

2 and Example 3), 0.03% eye drop containing Compound B (prepared in Example 4), 0.1% eye drop and 0.03% eye drop containing Compound C (each prepared in Example 5 and Example 6) and 0.03% eye drop containing Compound D (prepared in Example 7) were used.

5 Experiment method

[0112] Japanese white rabbits (body weight about 2 kg) purchased from Japan Laboratory Animals, INC. were used. These animals were bred in a breeding chamber set to temperature 23±3°C, humidity 55±10% and fed on limited amount of 100 g a day of a solid feed (Labo R Stock, Nihon-Nosan Kogyo K.K.). They were allowed free access to tap water. The rabbits were placed in a holding box for 5 hr a day for acclimation from 2 days prior to the test. The rabbits that showed steady intraocular pressure as measured by a tonometer [pneumatonograph (manufactured by Alcon Lab. Inc.)] were selected and used for the test. After measurement of the initial value of the intraocular pressure, various eye drops (20 µl) were instilled into one eye, and a base, which was one of various eye drops except the test drug, was instilled into the other eye in the same manner and taken as the control eye. The intraocular pressure was measured with time at 30, 60, 90, 120, 150 and 180 min after instillation and thereafter at one hour intervals until the intraocular pressure returned to the initial value, and the duration of the effect was examined.

Experiment result

[0113] The effects of eye drops containing each test drug at a concentration of 0.1% on the normal intraocular pressure are shown in Fig. 4 (Examples 2, 5). The effects of eye drops containing each test drug at a concentration of 0.03% on the normal intraocular pressure are shown in Fig. 5 (Examples 3, 4) and Fig. 6 (Examples 6, 7). In every case, a significant intraocular pressure lowering effect was found. In particular, Compound A (Examples 2, 3) showed an intraocular pressure lowering effect in early stages after instillation and Compound D (Example 7) showed a marked and long lasting intraocular pressure lowering effect.

Experimental Example 5: effect on of blood flow of normal optic disc of white rabbits

Test drug

[0114]

Compound A (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane 2HCl 1H₂O
Compound C (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide 2HCl

[0115] In this experiment, 0.1% eye drop containing Compound A (prepared in Example 2) and 0.1% eye drop containing Compound C (prepared in Example 5) were used.

Experiment method

[0116] Japanese white rabbits (body weight about 2 kg) purchased from Japan Laboratory Animals, INC. were used. These animals were bred in a breeding chamber set to temperature 23±3°C, humidity 55±10% and fed on limited amount of 100 g a day of a solid feed (Labo R Stock, Nihon-Nosan Kogyo K.K.). They were allowed free access to tap water. In the same manner as in Example 4, each test drug was administered. Using laser speckle microcirculation analyzer, the blood flow of optic disc was measured at 30, 60, 90, 120, 150 and 180 min after instillation and thereafter at one hour intervals till 300 min after the instillation.

Experiment result

[0117] The results are shown in Fig. 7. In every case, a significant blood flow increasing action was observed from 30 min after instillation. In particular, when Compound A (Example 2) was instilled, the effect was more long-lasting.

[0118] In consideration of the results of Experimental Example 2, this optic disc blood flow increasing action was considered to be attributable to vasodilation caused by dephosphorylation of vascular smooth muscle myosin light chain due to the activation of myosin phosphatase by a compound having a Rho kinase inhibitory activity (Masayoshi Uehata, et al., Nature 389, 990-994, 1997) and the accompanying increase in ophthalmic perfusion pressure (blood pressure - intraocular pressure).

Experimental Example 6: ophthalmic disorder caused by 8-time-a-day instillation to white rabbitsTest drug

5 [0119]

Compound A (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane 2HCl 1H₂O
 Compound C (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide 2HCl

10 [0120] The test drugs, Compound A and Compound C, were each dissolved in the following base at a concentration of 0.125, 0.25, 0.5 and 1.0% and adjusted to pH 7 for use in this experiment.

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| Formulation of base | |
|--------------------------------------|--------------------|
| Sodium dihydrogenphosphate 2 hydrate | 0.1 g |
| Sodium chloride | 0.9 g |
| Sodium hydroxide | appropriate amount |
| distilled water for injection | appropriate amount |
| Total amount | 100 ml |

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Experiment method

25 [0121] Japanese white rabbits (body weight about 2 kg) purchased from Japan Laboratory Animals, INC. were used. These animals were bred in a breeding chamber set to temperature 23±3°C, humidity 55±10% and fed on limited amount of 100 g a day of a solid feed (Labo R Stock, Nihon-Nosan Kogyo K.K.). They were allowed free access to tap water. Instillation: Using a micropipet, each test drug (100 µl) was instilled into the right eye of each animal 8 times at one hour intervals. Into the left eye was instilled a base in the same manner. Observation: anterior segment of the eye was macroscopically observed before instillation and 30 min after 2nd, 4th, 6th and 8th administrations, according to the macroscopic criteria for ocular lesions as shown in Table 1 (Naruyuki Fukui, Fumihiko Ikemoto, *Gendai no Rinshou* 4, 277-289, 1970). In addition, corneal staining spot was observed before instillation and after 8th administration.

30 [0122] The results of macroscopic observation of the anterior segment of the eye upon administration of Compound A are shown in Table 2 and the results of macroscopic observation of the anterior segment of the eye upon administration of Compound C are shown in Table 3.

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Table 1. Macroscopic criteria for ocular lesions in rabbits

| | | | |
|----|--|--|-----|
| 5 | Cornea | B) Edema of palpebral conjunctiva | |
| | A. Degree of opacity | | |
| | • No opacity (normal) | • No swelling | 0 |
| 10 | • Scattered or diffuse areas, details of iris clearly visible | • Slight edematous tendency | 0.5 |
| | • Easily discernible translucent areas, details of iris slightly obscured | • Swelling above normal | 1 |
| | • Opalescent areas, no details of iris visible, size of pupil barely discernible | • Obvious swelling with partial eversion of lids | 2 |
| 15 | • Opaque, iris invisible | • Swelling with lids about half closed | 3 |
| | | • Swelling with lids about half closed to completely closed | 4 |
| 20 | B. Area of opacity | C) Redness of bulbar conjunctiva | |
| | • One quarter (or less) but not zero | • No injection | 0 |
| | • Greater than one quarter but less than half | • Slight vasodilatation of circumcorneal vessels | 0.5 |
| 25 | • Greater than half but less than three quarters | • More prominent vasodilation | 1 |
| | • Greater than three quarters, up to whole area | • Marked vasodilation of vessels coursing toward the palpebral edge or the vessels tinged markedly red | 2 |
| 30 | IRIS | D. Nictitating membrane | |
| | Values | • No injection | 0 |
| | • Normal | • Tendency toward vasodilation and edema | 0.5 |
| | • Folds above normal congestion, swelling circumcorneal injection (any or all of these or any combination), iris reacts to light (sluggish reaction is positive) | • More prominent vasodilation, the palpebral edge tinged with red | 1 |
| 35 | • No reaction to light, hemorrhage, gross destruction (any or all of these) | • Very marked vasodilation, the whole nictitating membrane tinged with red | 2 |
| 40 | Conjunctiva | E) Discharge | |
| | A. Redness of palpebral conjunctiva | • No discharge | 0 |
| | • No injection | • Any amount different from normal (does not include small amounts observed in inner canthus) | 1 |
| | • Mucosa tinged very slightly with red, a slight vasodilation in the palpebral edge | • Discharge with moistening of the lids and hair just adjacent to lids | 2 |
| 45 | • Obvious injection above normal, mucosa tinged more definitely with red, prominent swelling | • Discharge with moistening of the lids and hair, and considerable are around the eye | 3 |
| | • Mucosa tinged very markedly with red, slightly indistinct peripheral vessels | | |
| | • Diffuse beefy red (more severe than 2) | | |

Table 2

| Scores of ocular lesions in rabbits administered with compound A (mean of three eyes) | | | | | | |
|---|--------|---------------------------------|----------------------|------|------|------|
| | | Item for scoring ocular lesions | Instillation | | | |
| | | | Before | 2nd | 4th | 6th |
| 5 | 0.125% | Cornea | Degree | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 |
| | | Iris Conjunctiva | Values | 0 | 0 | 0 |
| | | | Palpebral redness | 0 | 0.17 | 0 |
| | | | Palpebral edema | 0 | 0 | 0.33 |
| | | | Bulbar redness | 0 | 0.33 | 0.33 |
| | | | Nictitating membrane | 0 | 0 | 0 |
| | | | Discharge | 0 | 0 | 0.17 |
| | | Total score | | 0 | 0.50 | 1.99 |
| 10 | 0.25% | Cornea | Degree | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 |
| | | Iris Conjunctiva | Values | 0 | 0 | 0 |
| | | | Palpebral redness | 0 | 0.17 | 0 |
| | | | Palpebral edema | 0 | 0 | 0.17 |
| | | | Bulbar redness | 0 | 0.50 | 0.50 |
| | | | Nictitating membrane | 0 | 0.17 | 0.50 |
| | | | Discharge | 0 | 0 | 0.50 |
| | | Total score | | 0 | 0.84 | 1.00 |
| 15 | 0.5% | Cornea | Degree | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 |
| | | Iris Conjunctiva | Values | 0 | 0 | 0 |
| | | | Palpebral redness | 0 | 0.17 | 0.17 |
| | | | Palpebral edema | 0 | 0.17 | 0.17 |
| | | | Bulbar redness | 0.17 | 0.50 | 0.50 |
| | | | Nictitating membrane | 0 | 0 | 0.50 |
| | | | Discharge | 0 | 0 | 0.33 |
| | | Total score | | 0.17 | 0.49 | 1.50 |
| 20 | 0.5% | Iris Conjunctiva | Discharge | 0 | 0.33 | 0.33 |
| | | | Total score | 0 | 0.50 | 1.99 |
| | | | | | | 1.33 |
| | | Cornea | Degree | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0 |
| | | | Palpebral redness | 0 | 0.17 | 0 |
| | | | Palpebral edema | 0 | 0 | 0.17 |
| | | | Bulbar redness | 0 | 0.50 | 0.50 |
| | | | Nictitating membrane | 0 | 0.17 | 0.50 |
| | | | Discharge | 0 | 0 | 0.50 |
| | | | Total score | 0 | 0.84 | 1.00 |
| 25 | 0.5% | Iris Conjunctiva | Discharge | 0 | 0.17 | 0.33 |
| | | | Total score | 0 | 0.50 | 1.50 |
| | | | | | | 1.66 |
| | | Cornea | Degree | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0 |
| | | | Palpebral redness | 0 | 0.17 | 0.17 |
| | | | Palpebral edema | 0 | 0.17 | 0.17 |
| | | | Bulbar redness | 0 | 0.50 | 0.50 |
| | | | Nictitating membrane | 0 | 0.17 | 0.50 |
| | | | Discharge | 0 | 0 | 0.50 |
| | | | Total score | 0 | 0.84 | 1.00 |
| 30 | 0.5% | Iris Conjunctiva | Discharge | 0 | 0.17 | 0.33 |
| | | | Total score | 0 | 0.50 | 1.50 |
| | | | | | | 1.66 |
| | | Cornea | Degree | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0 |
| | | | Palpebral redness | 0 | 0.17 | 0.17 |
| | | | Palpebral edema | 0 | 0.17 | 0.17 |
| | | | Bulbar redness | 0 | 0.50 | 0.50 |
| | | | Nictitating membrane | 0 | 0.17 | 0.50 |
| | | | Discharge | 0 | 0 | 0.50 |
| | | | Total score | 0 | 0.84 | 1.00 |
| 35 | 0.5% | Iris Conjunctiva | Discharge | 0 | 0.17 | 0.67 |
| | | | Total score | 0 | 0.50 | 1.50 |
| | | | | | | 1.66 |
| | | Cornea | Degree | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0 |
| | | | Palpebral redness | 0 | 0.17 | 0.17 |
| | | | Palpebral edema | 0 | 0.17 | 0.17 |
| | | | Bulbar redness | 0.17 | 0.50 | 0.50 |
| | | | Nictitating membrane | 0 | 0 | 0.50 |
| | | | Discharge | 0 | 0 | 0.33 |
| | | | Total score | 0.17 | 0.49 | 1.50 |
| 40 | 0.5% | Iris Conjunctiva | Discharge | 0 | 0.17 | 0.67 |
| | | | Total score | 0 | 0.50 | 1.50 |
| | | | | | | 1.66 |
| | | Cornea | Degree | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0 |
| | | | Palpebral redness | 0 | 0.17 | 0.17 |
| | | | Palpebral edema | 0 | 0.17 | 0.17 |
| | | | Bulbar redness | 0.17 | 0.50 | 0.50 |
| | | | Nictitating membrane | 0 | 0 | 0.50 |
| | | | Discharge | 0 | 0 | 0.33 |
| | | | Total score | 0.17 | 0.49 | 1.50 |
| 45 | 0.5% | Iris Conjunctiva | Discharge | 0 | 0.17 | 0.67 |
| | | | Total score | 0 | 0.50 | 1.50 |
| | | | | | | 1.66 |
| | | Cornea | Degree | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0 |
| | | | Palpebral redness | 0 | 0.17 | 0.17 |
| | | | Palpebral edema | 0 | 0.17 | 0.17 |
| | | | Bulbar redness | 0.17 | 0.50 | 0.50 |
| | | | Nictitating membrane | 0 | 0 | 0.50 |
| | | | Discharge | 0 | 0 | 0.33 |
| | | | Total score | 0.17 | 0.49 | 1.50 |

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Table 2 (continued)

| Scores of ocular lesions in rabbits administered with compound A (mean of three eyes) | | | | | | | |
|---|---------------------------------|----------------------|--------------|------|------|------|-------|
| | Item for scoring ocular lesions | | Instillation | | | | |
| | | | Before | 2nd | 4th | 6th | 8th |
| 1.0% | Cornea | Degree | 0 | 0 | 0 | 0 | 0 |
| | | Area | 0 | 0 | 0 | 0 | 0 |
| | Iris Conjunctiva | Values | 0 | 0 | 0 | 0 | 0 |
| | | Palpebral redness | 0.17 | 0.50 | 0.50 | 0.83 | 2.17 |
| | | Palpebral edema | 0 | 0.67 | 0.67 | 1.33 | 3.00 |
| | | Bulbar redness | 0 | 0.50 | 0.50 | 1.17 | 1.50 |
| | | Nictitating membrane | 0 | 0.17 | 0.50 | 0.67 | 1.67 |
| | | Discharge | 0 | 0.33 | 0.67 | 1.67 | 2.33 |
| | Total score | | 0.17 | 2.17 | 2.84 | 5.67 | 10.67 |

Table 3

| Scores of ocular lesions in rabbits administered with compound C (mean of three eyes) | | | | | | | |
|---|---------------------------------|----------------------|--------------|------|------|------|------|
| | Item for scoring ocular lesions | | Instillation | | | | |
| | | | Before | 2nd | 4th | 6th | 8th |
| 0.125% | Cornea | Degree | 0 | 0 | 0 | 0 | 0 |
| | | Area | 0 | 0 | 0 | 0 | 0 |
| | Iris Conjunctiva | Values | 0 | 0 | 0 | 0 | 0 |
| | | Palpebral redness | 0 | 0 | 0 | 0.17 | 0.33 |
| | | Palpebral edema | 0 | 0 | 0 | 0.17 | 0.33 |
| | | Bulbar redness | 0 | 0 | 0.50 | 0.17 | 0.50 |
| | | Nictitating membrane | 0 | 0 | 0.33 | 0.33 | 0.50 |
| | | Discharge | 0 | 0 | 0.17 | 0.50 | 0 |
| | Total score | | 0 | 0 | 0.83 | 0.84 | 1.66 |
| 0.25% | Cornea | Degree | 0 | 0 | 0 | 0 | 0 |
| | | Area | 0 | 0 | 0 | 0 | 0 |
| | Iris Conjunctiva | Values | 0 | 0 | 0 | 0 | 0 |
| | | Palpebral redness | 0 | 0 | 0.33 | 0.33 | 0 |
| | | Palpebral edema | 0 | 0 | 0 | 0.17 | 0 |
| | | Bulbar redness | 0 | 0.33 | 0.33 | 0.50 | 0.67 |
| | | Nictitating membrane | 0 | 0.33 | 0.50 | 0.33 | 1.33 |
| | | Discharge | 0 | 0 | 0 | 0.67 | 1.00 |
| | Total score | | 0 | 0.66 | 1.50 | 2.83 | 3.00 |

Table 3 (continued)

| Scores of ocular lesions in rabbits administered with compound C (mean of three eyes) | | | | | | | |
|---|------|---------------------------------|----------------------|-----|------|------|------|
| | | Item for scoring ocular lesions | Instillation | | | | |
| | | | Before | 2nd | 4th | 6th | |
| 5 | 0.5% | Cornea | Degree | 0 | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0.33 | 0 |
| | | | Palpebral redness | 0 | 0 | 0.33 | 0.33 |
| | | | Palpebral edema | 0 | 0 | 0.33 | 0.33 |
| | | | Bulbar redness | 0 | 0.50 | 0.50 | 0.67 |
| | | | Nictitating membrane | 0 | 0.50 | 0.33 | 1.00 |
| | | | Discharge | 0 | 0 | 0.17 | 1.00 |
| 10 | 1.0% | Iris Conjunctiva | Total score | 0 | 1.00 | 1.99 | 3.83 |
| | | | Degree | 0 | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0.67 | 1.00 |
| | | | Palpebral redness | 0 | 0.17 | 0.50 | 0.50 |
| | | | Palpebral edema | 0 | 0 | 0.17 | 0.50 |
| | | | Bulbar redness | 0 | 0.50 | 0.50 | 0.67 |
| | | | Nictitating membrane | 0 | 0.50 | 0.50 | 0.33 |
| 15 | 20 | Cornea | Discharge | 0 | 0 | 0.17 | 1.00 |
| | | | Total score | 0 | 1.00 | 1.99 | 3.83 |
| | | | Degree | 0 | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0.67 | 1.00 |
| | | | Palpebral redness | 0 | 0.17 | 0.50 | 0.50 |
| | | | Palpebral edema | 0 | 0 | 0.17 | 0.50 |
| | | | Bulbar redness | 0 | 0.50 | 0.50 | 0.67 |
| 25 | 30 | Iris Conjunctiva | Nictitating membrane | 0 | 0.50 | 0.50 | 0.33 |
| | | | Discharge | 0 | 0 | 0.17 | 1.00 |
| | | | Total score | 0 | 1.17 | 2.34 | 3.83 |
| | | | Degree | 0 | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0.67 | 1.00 |
| | | | Palpebral redness | 0 | 0.17 | 0.50 | 0.50 |
| | | | Palpebral edema | 0 | 0 | 0.17 | 0.50 |
| 35 | 40 | Cornea | Bulbar redness | 0 | 0.50 | 0.50 | 0.67 |
| | | | Nictitating membrane | 0 | 0.50 | 0.50 | 0.33 |
| | | | Discharge | 0 | 0 | 0.17 | 1.00 |
| | | | Total score | 0 | 1.17 | 2.34 | 3.83 |
| | | | Degree | 0 | 0 | 0 | 0 |
| | | | Area | 0 | 0 | 0 | 0 |
| | | | Values | 0 | 0 | 0.67 | 1.00 |
| | | | Palpebral redness | 0 | 0.17 | 0.50 | 0.50 |

[0123] According to the observation of corneal staining spot, the administration of Compound A at any concentration did not lead to abnormalities. In contrast, when Compound C was administered, 0.25% instillation caused abnormality in two eyes, 0.5 and 1.0% instillations caused abnormality in all eyes at corneal epithelium. However, 0.125% instillation did not cause particular abnormality.

Industrial Applicability

[0124] In the agent for the prophylaxis and treatment of glaucoma of the present invention, since a compound having a Rho kinase inhibitory activity shows an intraocular pressure lowering effect, an optic disc blood flow improving effect and an aqueous outflow promoting effect, the agent is useful for the prophylaxis and treatment of various types of glaucoma, such as primary open angle glaucoma, normal pressure glaucoma, hypersecretion glaucoma, ocular hypertension, acute angle closure glaucoma, chronic angle closer glaucoma, plateau iris syndrome, combined-mechanism glaucoma, steroid glaucoma, capsular glaucoma, pigmentary glaucoma, secondary glaucoma associated with amyloidosis, neovascular glaucoma, malignant glaucoma and the like.

[0125] Inasmuch as the compound having a Rho kinase inhibitory activity inhibits contraction of ciliary muscle, it is useful as an agent for the prophylaxis and treatment of asthenopia and pseudomyopia and the like caused by sustained abnormal tension of ciliary muscle.

[0126] This application is based on a patent application Nos. 247762/1998 and 122960/1999 filed in Japan, the content of which is hereby incorporated by reference.

Claims

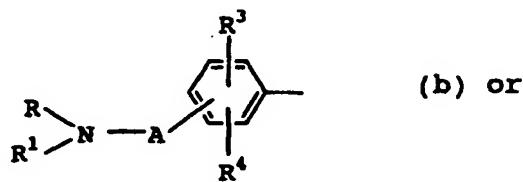
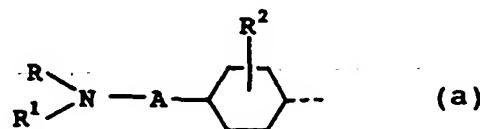
1. An agent for the prophylaxis and treatment of glaucoma, which comprises a compound having a Rho kinase inhibitory activity.

5 2. The agent for the prophylaxis and treatment of glaucoma of claim 1, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)

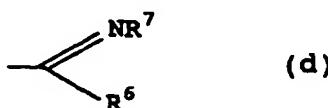


15 wherein

Ra is a group of the formula



40 R in the formulas (a) and (b),
45 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula



50 wherein R⁶ is hydrogen, alkyl or formula: -NR⁸NR⁹ wherein R⁸ and R⁹ are the same or different and each is hydrogen, alkyl, aralkyl or phenyl, R⁷ is hydrogen, alkyl, aralkyl, phenyl, nitro or cyano, or R⁶ and R⁷ in combination show a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

55 R¹ is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R and R¹ in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted

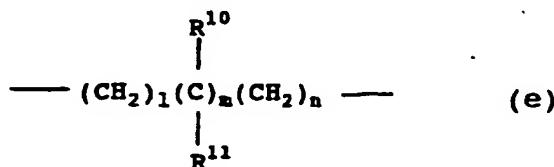
nitrogen atom,

 R^2 is hydrogen or alkyl, R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxy-carbonyl, carbamoyl, alkylcarbamoyl or azide, and

5

A is a group of the formula

10



15

wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-alkyl, carboxy or alkoxy-carbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

20

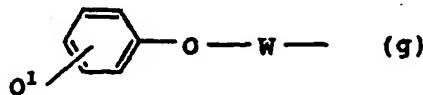
in the formula (c),

L is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula

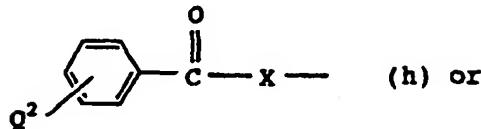
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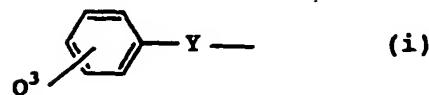
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wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxy-carbonylalkyl, α -aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,

55

 Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thiethylmethyl,

W is alkylene,

 Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,

X is alkylene,

 Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tet-

rahydropyridazin-6-yl;

and Y is a single bond, alkylene or alkenylene, and in the formula (C),

a broken line is a single bond or a double bond, and

5 R⁵ is hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;
 Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
 Rc is an optionally substituted heterocycle containing nitrogen,

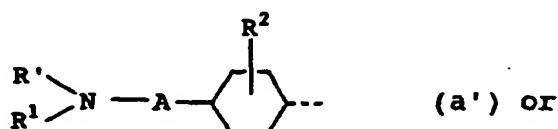
an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

10 3. The agent for the prophylaxis and treatment of glaucoma of claim 1 or claim 2, wherein the compound having a Rho kinase inhibitory activity is an aide compound of the following formula (I')

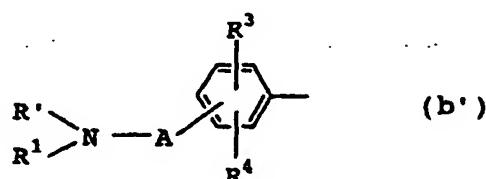


20 wherein

Ra' is a group of the formula wherein



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40

R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

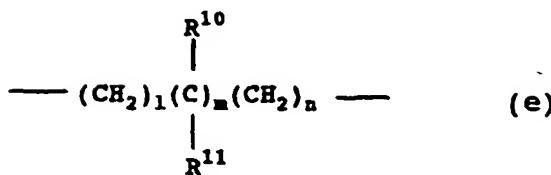
R¹ is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R' and R¹ in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R² is hydrogen or alkyl,

R³ and R⁴ are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkythio, aralkylthio, carboxy, alkoxy-carbonyl, carbamoyl, alkylcarbamoyl or azide, and

A is a group of the formula

55



10 wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-alkyl, carboxy or alkoxy carbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l , m and n are each 0 or an integer of 1-3,

15 Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
 Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

20 4. The agent for the prophylaxis and treatment of glaucoma of claim 1, wherein the compound having a Rho kinase inhibitory activity is (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid addition salt thereof.

25 5. The agent for the prophylaxis and treatment of glaucoma of claim 1, which is administered to a local site in the eye.

6. The agent for the prophylaxis and treatment of glaucoma of claim 5, which is in the form of an eye drop.

30 7. A pharmaceutical composition for the prophylaxis and treatment of glaucoma, which comprises a compound having a Rho kinase inhibitory activity and a pharmaceutically acceptable carrier.

8. The pharmaceutical composition for the prophylaxis and treatment of glaucoma of claim 7, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)



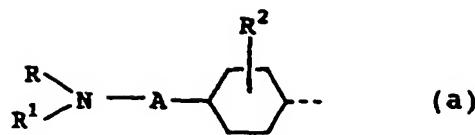
40 wherein

45 Ra is a group of the formula

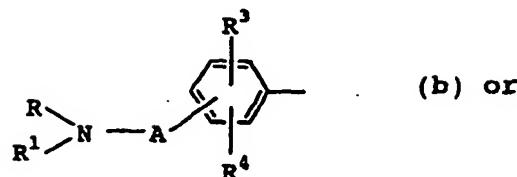
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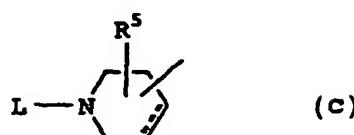


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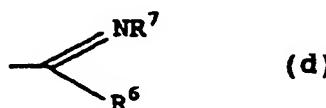
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20



in the formulas (a) and (b),
 25 R is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula

30



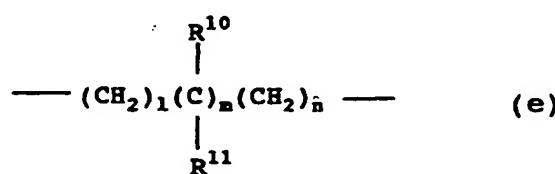
35 wherein R6 is hydrogen, alkyl or formula : -NR8NR9 wherein R8 and R9 are the same or different and each is hydrogen, alkyl, aralkyl or phenyl, R7 is hydrogen, alkyl, aralkyl, phenyl, nitro or cyano, or R6 and R7 in combination show a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

40 R1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R and R1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

45 R2 is hydrogen or alkyl,
 R3 and R4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkythio, aralkylthio, carboxy, alkoxy-carbonyl, carbamoyl, alkylcarbamoyl or azide, and

45 A is a group of the formula

50



55

wherein R10 and R11 are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-alkyl, carboxy or alkoxy-carbonyl, or R10 and R11 show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

in the formula (c),

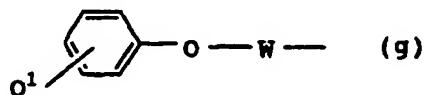
L is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula

5



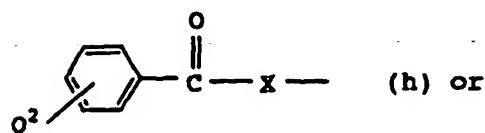
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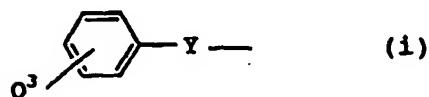


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35 wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxylalkyl, alkanoyloxyalkyl, alkoxy carbonylalkyl, α -aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl, Q¹ is hydrogen, halogen, hydroxy, aralkyloxy or thiethylmethyl,

W is alkylene,

Q² is hydrogen, halogen, hydroxy aralkyloxy,

X is alkylene,

Q³ is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl;

and Y is a single bond, alkylene or alkenylene, and in the formula (c),

a broken line is a single bond or a double bond, and

45 R⁵ is hydrogen, hydroxy, alkoxy, alkoxy carbonyloxy, alkanoyloxy or aralkyloxy carbonyloxy;

Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

50

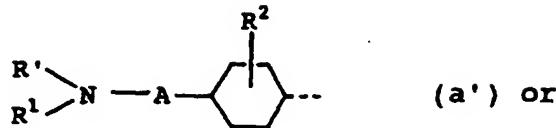
9. The pharmaceutical composition for the prophylaxis and treatment of glaucoma of claim 7 or claim 8, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I")

55

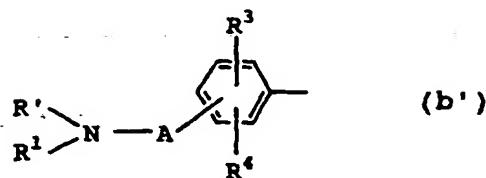


10 wherein

15 Ra' is a group of the formula



20



30

30 wherein

R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

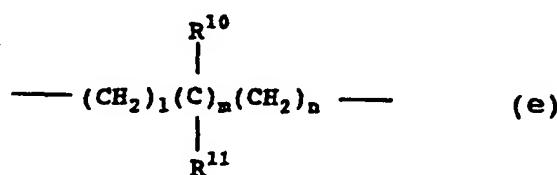
R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R' and R^1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R^2 is hydrogen or alkyl,

R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkythio, aralkylthio, carboxy, alkoxy-

40

A is a group of the formula



50

50 wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-alkyl, carboxy or alkoxy carbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l , m and n are each 0 or an integer of 1-3,

55

Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

10. The pharmaceutical composition for the prophylaxis and treatment of glaucoma of claim 7, wherein the compound having a Rho kinase inhibitory activity is (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid addition salt thereof.

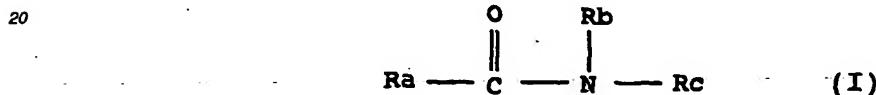
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11. The pharmaceutical composition for the prophylaxis and treatment of glaucoma of claim 7, which is for administration to local site in the eye.

10 12. The pharmaceutical composition for the prophylaxis and treatment of glaucoma of claim 11, which is in the form of an eye drop.

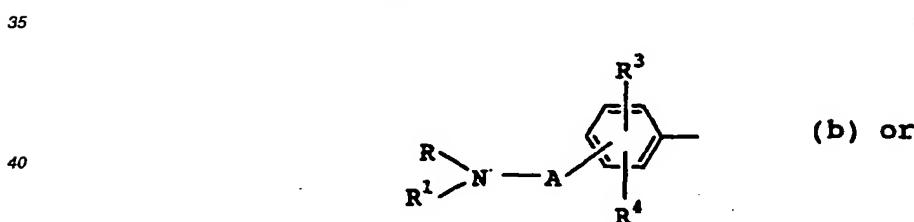
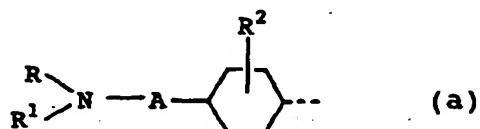
15 13. A method of the prophylaxis and treatment of glaucoma, which comprises administering an effective amount of a compound having a Rho kinase inhibitory activity to a patient.

14. The method of the prophylaxis and treatment of glaucoma of claim 13, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)

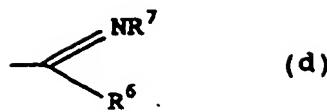


25
wherein

30 Ra is a group of the formula



50 R in the formulas (a) and (b),
55 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula



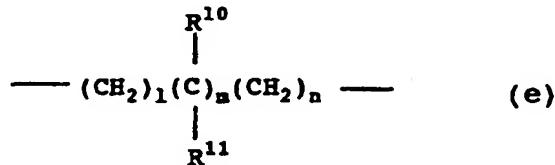
10 wherein R⁶ is hydrogen, alkyl or formula: -NR⁸NR⁹ wherein R⁸ and R⁹ are the same or different and each is hydrogen, alkyl, aralkyl or phenyl, R⁷ is hydrogen, alkyl, aralkyl, phenyl, nitro or cyano, or R⁶ and R⁷ in combination show a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

15 R¹ is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R and R¹ in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

20 R² is hydrogen or alkyl,

R³ and R⁴ are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkythio, aralkylthio, carboxy, alkoxy-carbonyl, carbamoyl, alkylcarbamoyl or azide, and

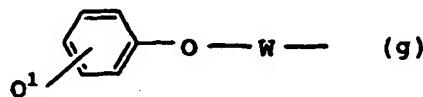
25 A is a group of the formula



30 wherein R¹⁰ and R¹¹ are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-alkyl, carboxy or alkoxy-carbonyl, or R¹⁰ and R¹¹ show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

35 in the formula (c),

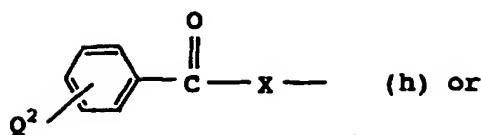
L is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula



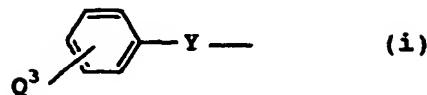
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15

wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxy carbonylalkyl, α -aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,

Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thiethylmethyl,

W is alkylene,

20

Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,

X is alkylene,

Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl;

and Y is a single bond, alkylene or alkenylene, and in the formula (c),

25

a broken line is a single bond or a double bond, and

R^5 is hydrogen, hydroxy, alkoxy, alkoxy carbonyloxy, alkanoyloxy or aralkyloxy carbonyloxy;

R^b is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

R^c is an optionally substituted heterocycle containing nitrogen,

30

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

15. The method of the prophylaxis and treatment of glaucoma of claim 13 or claim 14, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')

35



40

wherein

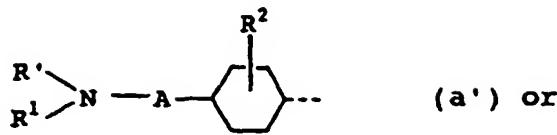
45

Ra' is a group of the formula

50

55

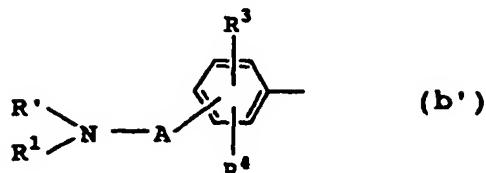
5



(a') or

10

15



(b')

wherein

20 R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

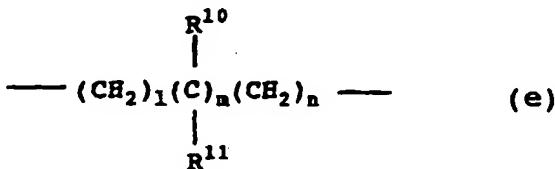
25 R¹ is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R' and R¹ in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

30 R² is hydrogen or alkyl,

R³ and R⁴ are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxy-carbonyl, carbamoyl, alkylcarbamoyl or azide, and

A is a group of the formula

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wherein R¹⁰ and R¹¹ are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-alkyl, carboxy or alkoxy-carbonyl, or R¹⁰ and R¹¹ show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

45 R_b is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
 R_c is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

16. The method of the prophylaxis and treatment of glaucoma of claim 13, wherein the compound having a Rho kinase inhibitory activity is (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid addition salt thereof.

55 17. The method of the prophylaxis and treatment of glaucoma of claim 13, wherein the administration to a patient is that to a local site in the eye.

18. The method of the prophylaxis and treatment of glaucoma of claim 17, wherein the administration to a patient is by

instillation.

19. Use of a compound having a Rho kinase inhibitory activity for the production of an agent for the prophylaxis and treatment of glaucoma.

5

20. The use of claim 19, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)

10



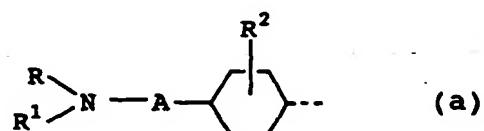
15

wherein

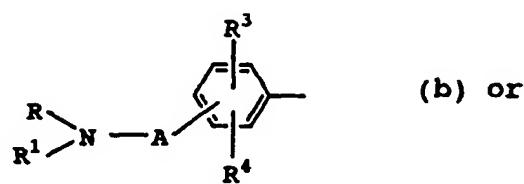
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Ra is a group of the formula

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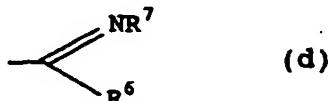
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45

R in the formulas (a) and (b), is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula

50



55

wherein R6 is hydrogen, alkyl or formula : -NR8NR9 wherein R8 and R9 are the same or different and each is hydrogen, alkyl, aralkyl or phenyl, R7 is hydrogen, alkyl, aralkyl, phenyl, nitro or cyano, or R6 and R7 in combination show a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent

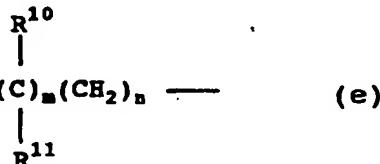
on the ring, or R and R¹ in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

5 R² is hydrogen or alkyl,

R³ and R⁴ are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkythio, aralkylthio, carboxy, alkoxy-

carbonyl, carbamoyl, alkylcarbamoyl or azide, and

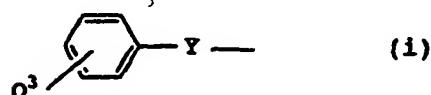
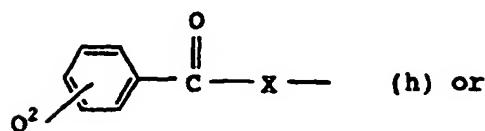
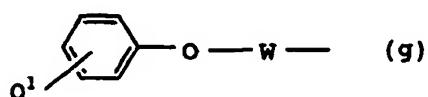
A is a group of the formula



wherein R¹⁰ and R¹¹ are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-
20 alkyl, carboxy or alkoxy carbonyl, or R¹⁰ and R¹¹ show a group which forms cycloalkyl in combination
and l, m and n are each 0 or an integer of 1-3,

in the formula (c),

L is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula



55 wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxycarbonylalkyl, α -aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,

Q¹ is hydrogen, halogen, hydroxy, aralkyloxy or thienylmethyl,

W is alkylene,

Q² is hydrogen, halogen, hydroxy or aralkyloxy,

X is alkylene,
 Q³ is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl;

and Y is a single bond, alkylene or alkenylene, and in the formula (c),
 a broken line is a single bond or a double bond, and

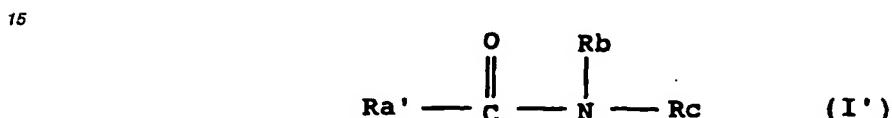
R⁵ is hydrogen, hydroxy, alkoxy, alkoxy carbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;

R^b is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

R^c is an optionally substituted heterocycle containing nitrogen,

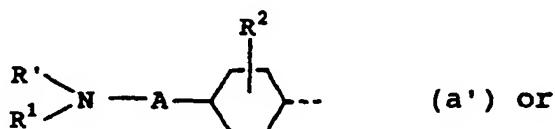
an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

21. The use of claim 19 or claim 20, wherein the compound having a Rho kinase is an amide compound of the following formula (I)

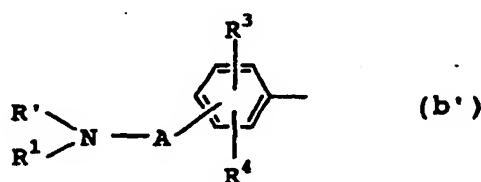


20
 wherein

25 R^{a'} is a group of the formula



30



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wherein

45 R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

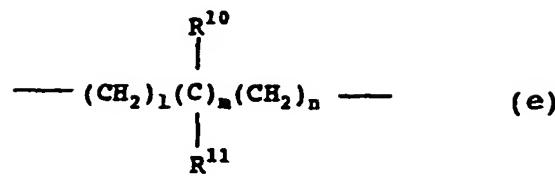
R¹ is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R' and R¹ in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R² is hydrogen or alkyl,

50 R³ and R⁴ are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxy-carbonyl, carbamoyl, alkylcarbamoyl or azide, and

A is a group of the formula

55



10 wherein R¹⁰ and R¹¹ are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxy-alkyl, carboxy or alkoxy carbonyl, or R¹⁰ and R¹¹ show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3.

15 Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

20 22. The use of claim 19, wherein the compound having a Rho kinase inhibitory activity is (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid addition salt thereof.

25 23. The use of claim 19, wherein the agent for the prophylaxis and treatment of glaucoma is for administration to a local site in the eye.

24. The use of claim 23, wherein the agent for the prophylaxis and treatment of glaucoma is in the form of an eye drop.

30 25. A commercial package comprising a pharmaceutical composition for the prophylaxis and treatment of glaucoma of any of claim 7 to claim 12, and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for the prophylaxis and treatment of glaucoma.

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FIG. 1

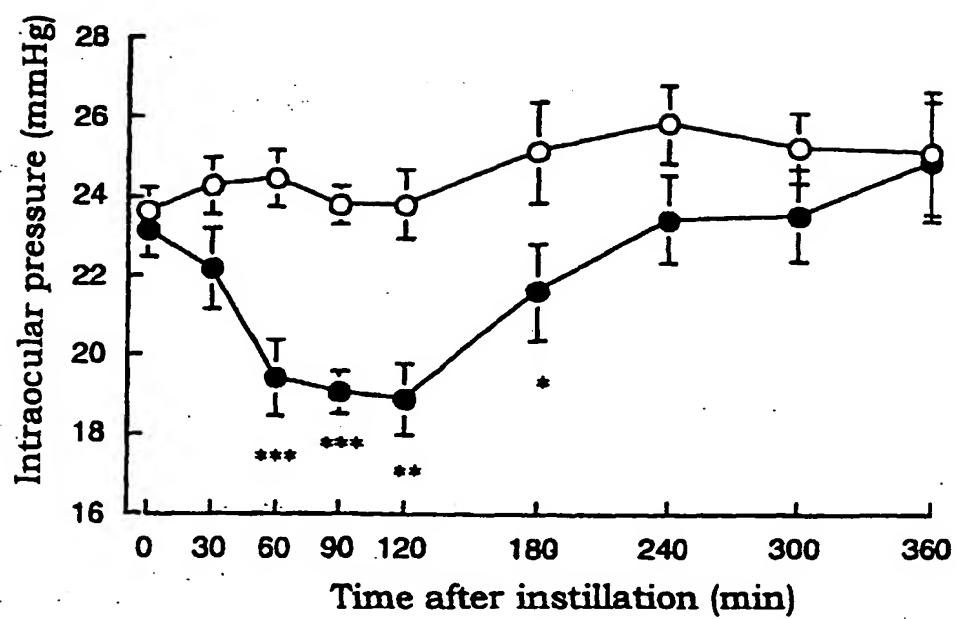


FIG. 2

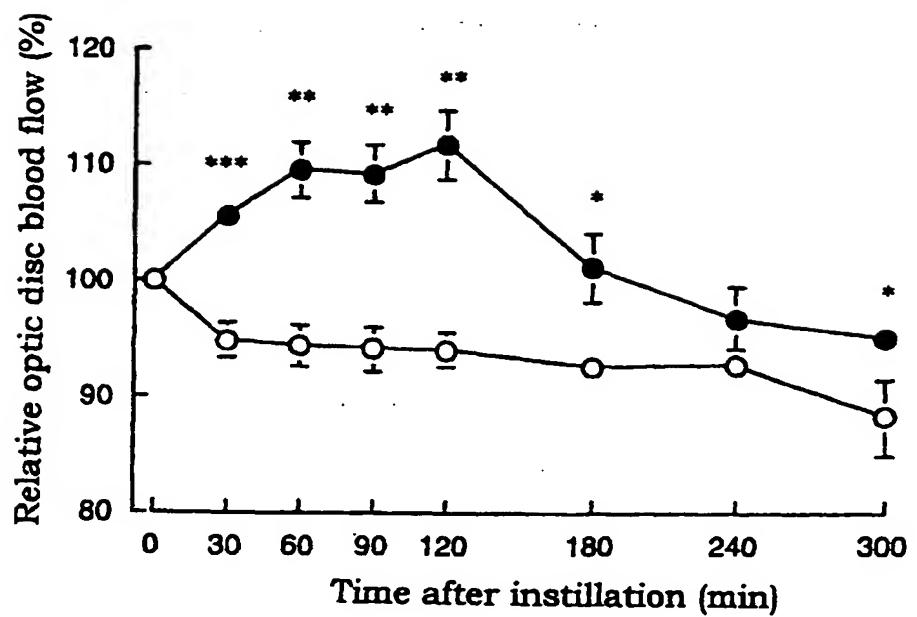


FIG. 3

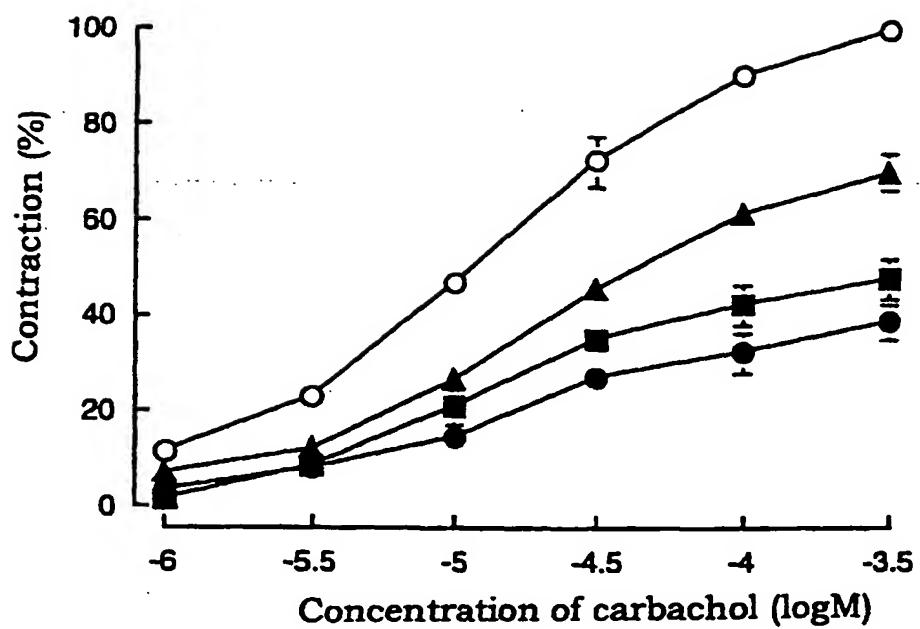


FIG. 4

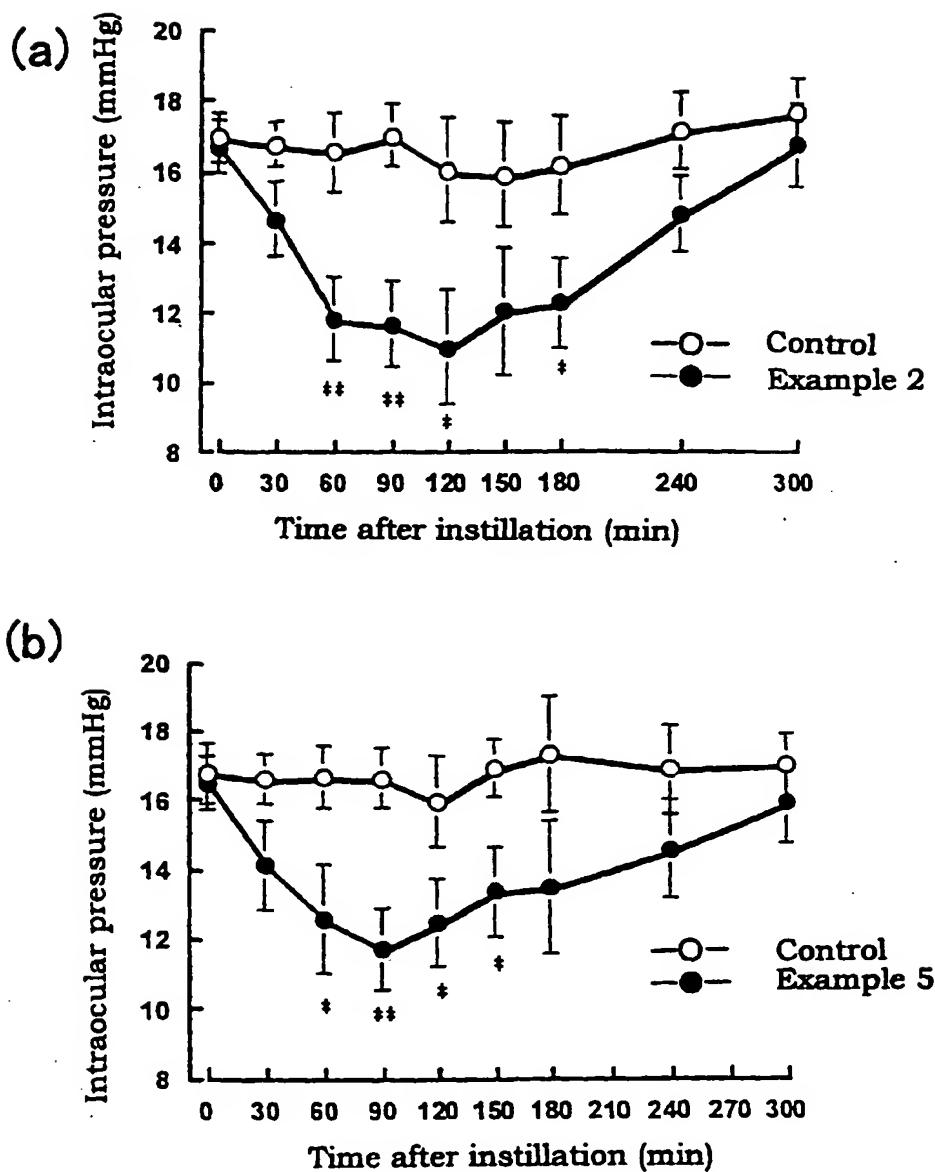


FIG. 5

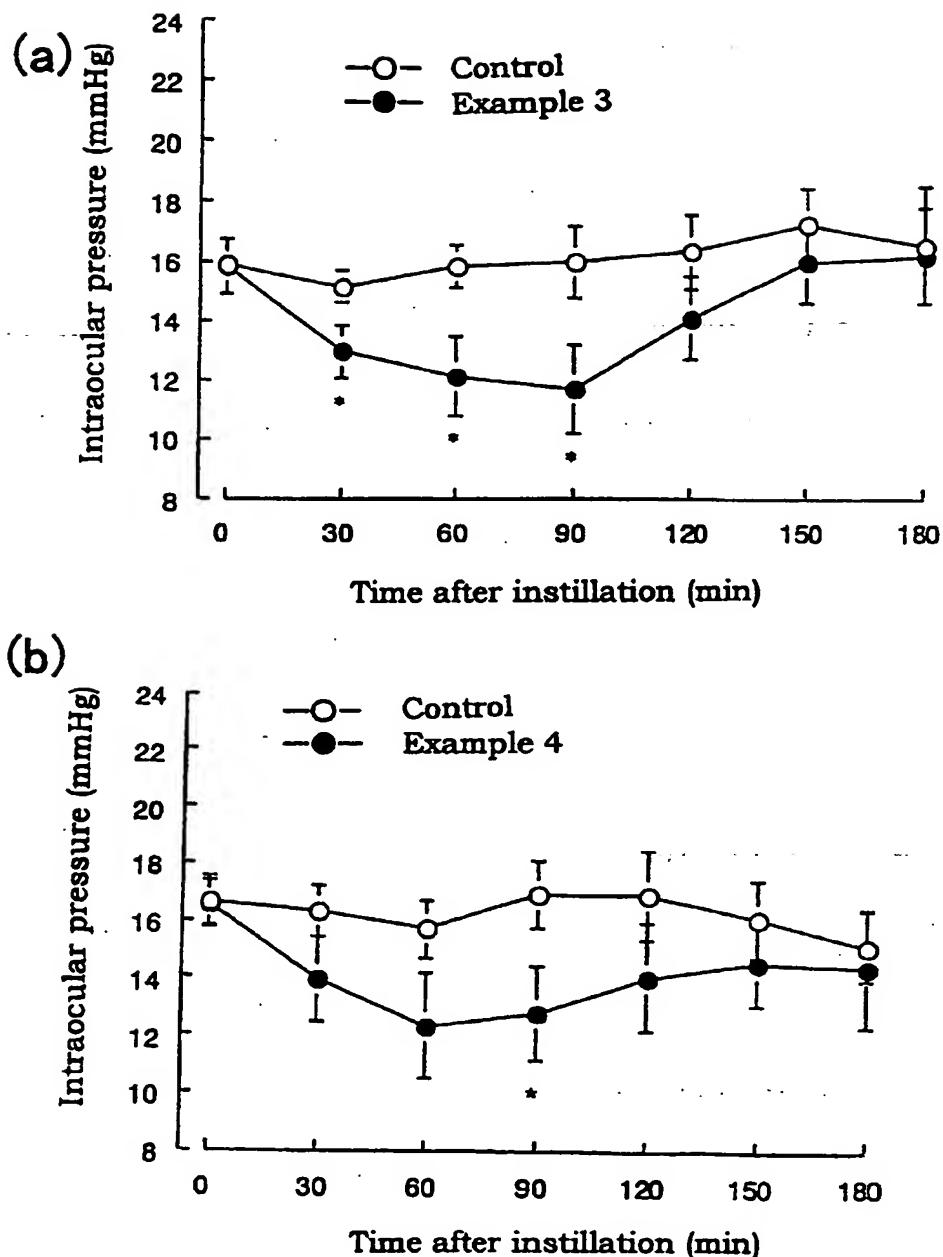


FIG. 6

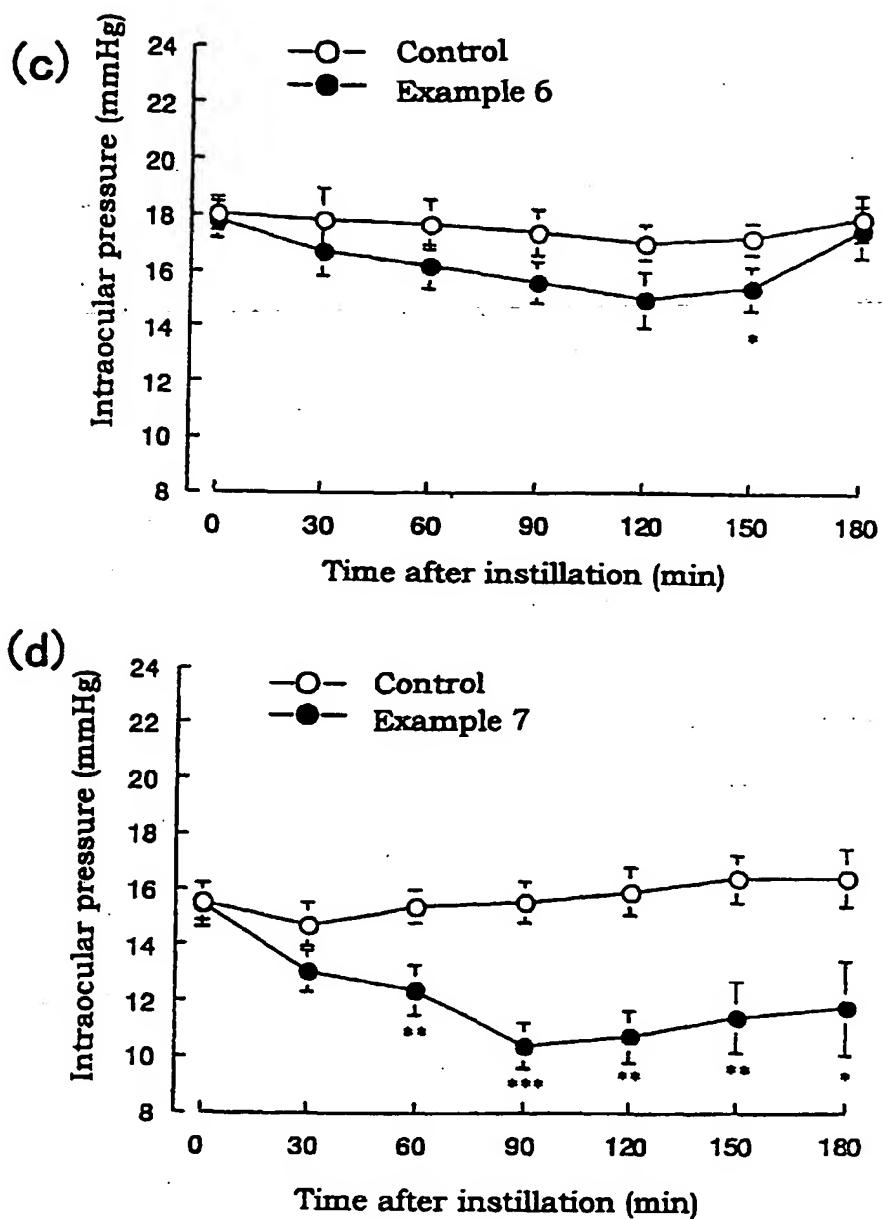
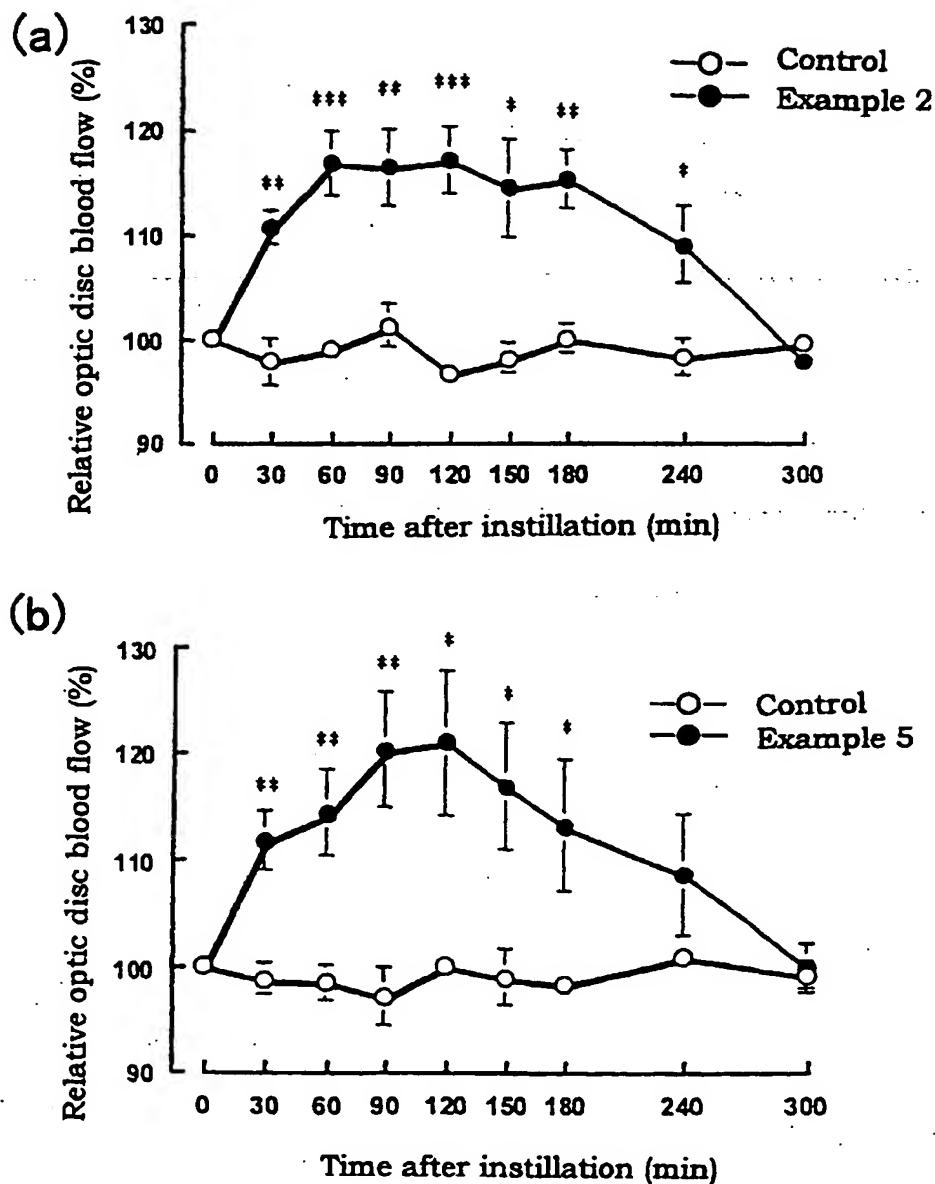


FIG. 7



| INTERNATIONAL SEARCH REPORT | | International application No. PCT/JP99/04403 |
|---|--|---|
| A. CLASSIFICATION OF SUBJECT MATTER Int.Cl' A61K45/00, A61K31/44, A61K31/445 | | |
| According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl' A61K45/00, A61K31/44, A61K31/445 | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS (STN), REGISTRY (STN), WPI (DIALOG), MEDLINE (STN) | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| Y | WO, 98/06433, A1 (Yoshitomi Pharmaceutical Industries, Ltd.), 19 February, 1998 (19. 02. 98), Claims ; page 4, lines 8 to 18 ; page 54, line 16 to page 55, line 21 & AU, 9737851, A & NO, 9900622, A & CZ, 9900460; A | 1-12, 19-25 |
| Y | JP, 10-113187, A (Kirin Brewery Co., Ltd.), 6 May, 1998 (06. 05. 98), Claims & US, 5906819, A | 1, 5-7, 11, 12, 19, 23-25 |
| A | | 2-4, 8-10, 20-22 |
| Y | JP, 8-198876, A (Yoshitomi Pharmaceutical Industries, Ltd.), 6 August, 1996 (06. 08. 96), Par. Nos. [0002], [0018] (Family: none) | 1-12, 19-25 |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex. | | |
| * Special categories of cited documents: 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'P' document published prior to the international filing date but later than the priority date claimed | | |
| Date of the actual completion of the international search 27 October, 1999 (27. 10. 99) | | Date of mailing of the international search report 9 November, 1999 (09. 11. 99) |
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/04403

| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| Y | JP, 8-504195, A (Yissum Research Development Co. of the Hebrew University of Jerusalem), 7 May, 1996 (07. 05. 96), Claims ; page 10, lines 7 to 20 & WO, 94/12466, A & EP, 670826, A1 & US, 5618955, A | 1-12, 19-25 |
| Y | JP, 7-504099, A (CIBA Vision AG, Hettoringen), 11 May, 1995 (11. 05. 95), Claims ; Examples & WO, 93/15732, A & EP, 626849, A & AU, 9337224, A & ZA, 9301063, A & NO, 9402756, A | 1-12, 19-25 |
| Y | JP, 5-213940, A (Syntex (U.S.A.) Inc.), 24 August, 1993 (24. 08. 93), Claim 33 ; Examples & US, 5250547, A & EP, 529654, A1 & NO, 9203382, A & CA, 2077098, A & FI, 9203872, A | 1-12, 19-25 |

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INTERNATIONAL SEARCH REPORT

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| International application No. PCT/JP99/04403 |
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 13 to 18

because they relate to subject matter not required to be searched by this Authority, namely:

These claims pertain to methods for treatment of the human body by surgery or therapy (provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT).

2. Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 44(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

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